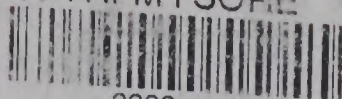


# THE BODY FLUIDS

BASIC PHYSIOLOGY & PRACTICAL THERAPEUTICS

J. R. ELKINTON, M.D. and T. S. DANOWSKI, M.D.

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*The Body Fluids*







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## BASIC PHYSIOLOGY AND PRACTICAL THERAPEUTICS

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To our teachers and to our many colleagues, and especially to

JOHN P. PETERS and ALEXANDER W. WINKLER

## PREFACE

During the past three decades many advances in medical science have profoundly changed the nature of medical practice. Of these advances one of the most far-reaching has been the application of laboratory methods to the diagnosis and treatment of sick people. This has come about through the development of chemical methods for the analysis of biological materials, and through an increased interest in the application of concepts of basic physiology and biochemistry to the study of the diseased organism. The results of this development have been mutually beneficial to the basic sciences and clinical medicine and have greatly increased our knowledge of disease processes and our ability to deal with them. But it has also resulted in the fact that the physician is faced with an enormous and steadily increasing amount of physiological information and with complex chemical tools for diagnosis and treatment. He also finds some diversity of opinion among the experts in regard to the use of these chemical tools. It is not surprising, therefore, that physicians old and young admit to a certain amount of confusion in their attempts to master these tools for use in their profession, and express a need for help in separating the more important from the less important and proved fact from mere opinion.

This monograph is an attempt to meet this need in respect to one field of clinical medicine, namely, disturbances of body fluid dynamics. No book by one author or group of authors can cover this subject either completely or finally, for new knowledge is constantly being acquired and fresh insight gained. Furthermore, the range of clinical disturbances included in this subject is so wide that the clinical experience of no two groups of authors is likely to be identical. Nevertheless, because of the need stated above, it seems worthwhile to attempt to summarize present knowledge in the field and in the light of this knowledge to analyze the experience of one group of workers.

The plan of the monograph is to present first a discussion of fundamental concepts of physiology and biochemistry in this field, utilize these principles in presentation of common denominators in clinical problems, discuss specific disease entities, and end with practicalities in assessing and correcting disorders of body fluids. In this way it is hoped that the book will be of value both to the student of physiology and to the clinician seeking practical help in the treatment of his patients; to the former it may serve, at least, as an annotated bibliography.

We are grateful to our many colleagues, past and present, at the University of Pennsylvania and the University of Pittsburgh, whose critical



judgment was helpful in the preparation of this volume. In particular we wish to acknowledge the assistance of Doctors E. S. Barker, L. W. Bluemle, Jr., J. R. Brobeck, T. M. Chalmers, J. K. Clark, E. B. Fergus, L. Greenman, A. G. Hills, K. Hofmann, E. J. Huth, M. Iunes, F. M. Mateer, F. H. McCutcheon, I. A. Mirsky, C. Moses, Jr., J. H. Peters, J. E. Rhoads, B. Shapiro, R. B. Singer, R. D. Squires, W. C. Stadie and F. A. Weigand.

The preparation of this volume would not have been possible without the devoted assistance of our secretaries: G. Bowers, A. D. Francis, M. B. Kyle, E. M. Roedel, and C. M. Whiteley. The copy was assembled by P. Wirth and the manuscript was checked by E. Trotter.

To our respective families we owe much for their forbearance and ever-present moral support.

Finally the authors wish to indicate their indebtedness for the financial support which was received from the Established Investigatorship of the American Heart Association (J. R. E.) and the Guggenheim Fellowship (T. S. D.) during the preparation of this text.

Philadelphia and  
Pittsburgh, Penna.  
April, 1955

J. R. E.  
T. S. D.

### Copyright Acknowledgements

We acknowledge with gratitude the permissions given to reproduce previously published figures and tables, by the following copyright owners: *Acta paediatrica*, The American College of Physicians, The American Medical Association, The American Physiological Society, The American Society for Clinical Investigation, Charles C. Thomas Co., *Clinical Science*, Grune and Stratton, Inc., The Harvey Society of New York, *The Irish Journal of Medical Science*, Lea and Febiger, C. V. Mosby Co., The Royal Irish Academy, W. B. Saunders Co., *The Yale Journal of Biology and Medicine* and *Diuretic Review*. We also wish to express our appreciation to the individual authors.

## Historical Preface

In the field of body fluid physiology, as in all other realms of knowledge, the achievements of the present rest firmly on the foundations of the past. Although the authors of this volume have made no attempt to review the subject in a historical manner, they wish to acknowledge their indebtedness to the pioneers of the past and to their contemporary colleagues who have obtained the data, developed the concepts, and made available the knowledge with which this book has been written.

The history of this field of endeavor may be divided conveniently into three periods of development: the century preceding World War I, the period between World Wars I and II (1918–1941), and the present period which began a little more than a decade ago during the last war. In the first of these periods, parenteral fluid therapy was pioneered by O'Shaughnessy and Latta (1832), biochemical analyses of the body fluids were begun by Schmidt and Bidder (1850), and physiologic concepts were developed and data obtained. The latter included the classic concept of *le milieu intérieur* as first promulgated by Claude Bernard in 1859, and the reciprocity of sodium and potassium transfers as observed by Bunge in 1873. The development of adequate analytical methods by such biochemists as Folin, Van Slyke, and Benedict prepared the way for the second period.

The period between the wars was perhaps ushered in by L. J. Henderson's contributions, in the field of physiological chemistry, to the understanding of the body's defence of neutrality, and by the application of that knowledge by Van Slyke, Peters, and others to clinical problems. This was the period of the birth and development of the field of clinical investigation in which such workers as Peters, Van Slyke, Gamble, Hartmann, Aub, Albright, Loeb, Butler, Newburgh, Darrow, McCance and many others brought the tools and concepts of the laboratory to the bedside of the patient. At the same time, in the disciplines of the so-called *basic sciences* of biochemistry and physiology, great advances were made in the understanding of the dynamics and regulation of the body fluids by such workers as Starling, Govaerts, Macallum, Adolf, Krogh, Richards, Landis, Hastings, Smith, Visscher, Conway, Gilman and others.

With the advent of World War II and the development of atomic energy, the study of water and electrolytes began a new era. This era has been characterized by a tremendous expansion of research activity. In 1934, 10 and 38 papers on subjects in this field appeared in the *Journal of Clinical Investigation* and the *American Journal of Physiology*, respectively;



in 1954 the corresponding numbers were 50 and 82 papers. This expansion has been due, at least in part, to the development of the flame photometer for the rapid determination of sodium and potassium and to the availability of radioactive isotopes for use as tracer constituents in the body fluids. The names of our contemporary fellow-workers in this field are too numerous to mention individually but will be found in the bibliographies throughout the book.

Prophecy has no place in a historical note but it would appear that we are on the threshold of a tremendous advance in knowledge of the fundamental processes of body fluid dynamics and in the application of that knowledge to the diagnosis and treatment of sick people. It is the hope of the authors that the present volume may assist this advance in knowledge and may contribute to the care of patients which will result from the application of that knowledge.



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PART I

*Basic Physiology and Fundamental  
Principles*





“Our stability is but balance, and wisdom lies  
in masterful administration of the unforeseen.”  
Robert Bridges in *The Testament of Beauty*

## Chapter 1

### BODY FLUID DYNAMICS

#### I. A Unified Concept

The body fluids consist of water as the solvent and many inorganic and organic substances as the solutes. The movements of the solvent as well as of the solutes are involved in the basic functioning of the living organism. As beginning or end products of the processes of metabolism, many of the solutes are in transit between the external environment and the organism or within the organism itself. Others are more stable components and constitute the milieu, within and without body cells, in which these transfers take place. The principal components of the body fluids are water, certain inorganic electrolytes, and proteins. These are the main concern of this work.

These “structural” components, however, constitute a *dynamic*, not a static, structure. Water is constantly entering and leaving the organism as well as being produced by oxidative processes within the cells. Electrolytes, which are the ionized or dissociated forms of inorganic and organic salts, are constantly moving between the organism and the environment as well as between various parts of the organism. Protein is in a continual state of turnover, being formed, transported and broken down within the body. In this dynamic sense, therefore, we are concerned both with “transfers” and with the active “distribution” of these components of the body fluids. These terms will appear frequently in this book and will bear this connotation.

The development of a dynamic concept of the body fluids requires careful consideration of the forces and processes that underlie the dynamic state. For this purpose we must turn to chemistry and physics for terms with which to describe these processes. In addition to describing chemical reactions of substances in the body, chemical concepts define such phenomena as the dissociation of solutes into an electrically neutral solution, the

diffusion of solutes between two *phases* or two solutions with a common solvent, and the osmotic pressure or force changes when solutes are restrained from diffusing from one phase to another. Physical concepts are needed to define the effect of hydrostatic pressures in these fluids and to describe the production, utilization and dissemination of energy by the system.

Concepts of chemistry and physics, however, are not adequate alone to describe the functioning of a living organism: physiological concepts are needed as well. The latter delineate not only the interaction of these chemical and physical forces between systems and organs within the body but also the relation of these forces to the processes that set them in motion, namely, the metabolic reactions that create energy gradients. Gradients of concentration, osmotic pressure, and hydrostatic pressure are developed by energy transfers that alter the concentration of solutes, that “actively” transport certain solutes, that create and maintain heads of hydrostatic pressure (principally through the cardiovascular system), and that lead to exchanges of solutes and solvents between the organism and the environment. As is true of many other biological and biochemical phenomena, healthy functioning of the body fluids consists in maintenance of a *dynamic steady state*. Thermodynamic equilibrium is that state in which energy exchanges have reached their lowest level and in a biological system is equivalent to death. As Stetten (1a, b) has put it succinctly: “the living organism may be differentiated at a biochemical level from the dead one by its capacity, when supplied with exogenous energy, to operate steadily yet in disequilibrium.” This is the dynamic steady state in which constancy of composition is maintained despite a continuous turnover of the many components of the system. This maintenance depends upon free energy. The energy to drive the engine is supplied immediately by such components as energy-rich adenosine triphosphate; ultimately it is derived exogenously from the sun by way of organic foodstuffs. Thus, as von Bertalanffy has pointed out (1c), the second law of thermodynamics is operative but in an open rather than a closed system. The chief characteristic of life in this complex set of interreactions of physical and chemical forces would appear to be that in such an open system the pattern of energy expenditure is not only orderly but also continually reproduced.<sup>1</sup>

These considerations touch upon the infinitely complex and basic problems of the nature of life as manifested in the integrated dynamics of body fluids. It is not the intention of the authors to elaborate on these problems; rather it is our purpose in this chapter to present to the reader a unified working concept of the dynamic interactions of the body fluids. This con-

<sup>1</sup> For a clear exposition of thermodynamics as applied to living systems, the reader is referred to the papers of Stetten (1a, b) and the book by Blum (1d).



cept must be “working” in the sense that the reader as a student and physician can use it as a background for the intelligent analysis of disturbances of the body fluids as he sees them in his patients. To this end the several phases or principal divisions of the body fluids will be described, the different types of chemical and physical forces in fluid systems will be illustrated, and the integration of these forces in the physiological system of the mammalian organism will be presented. For earlier comprehensive treatments of the subject the reader is referred to the writings of Peters, Gamble, McCance, Darrow, and others (2a-i).

## II. Fluid Phases in the Body

### A. In the Total Organism

In the organism as a whole the body fluids may be divided into two main phases, extracellular and intracellular (fig. 1-1). The intracellular phase consists of the water and the solutes within the cells of the various tissues and is the site of the metabolic processes of the body. The extracellular phase, as its name indicates, lies outside the cells and forms their aqueous environment within the body. To this phase Claude Bernard (3a) gave the name *le milieu interieur*, first recognizing that its function is to maintain a relatively constant environment within which cellular function can take place. In addition, the extracellular phase is the pathway between most of the cells of the body and the organs of exchange with the external world.

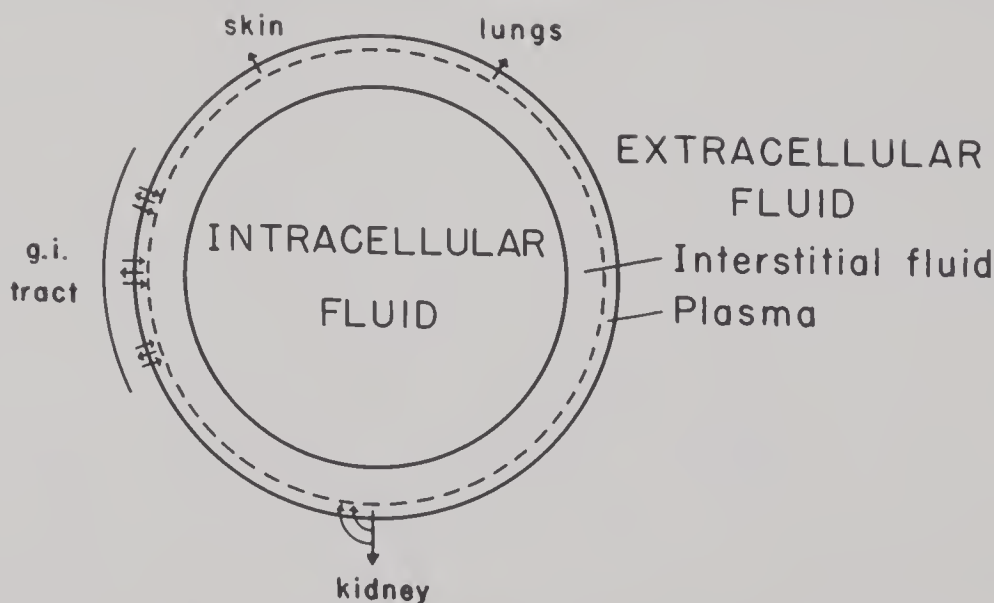


FIG. 1-1. COMPARTMENTS OF BODY FLUIDS

The diagram represents principal phases or compartments of the body fluids and the sites of exchange with the external environment. The extracellular fluid, consisting of an interstitial phase and the plasma, is involved in external transfers via the kidney, lungs, skin and gastrointestinal tract. The intracellular phase is two to three times as large as the extracellular phase.

The magnitude of the total body water is approximately 50 to 65 per cent of the body weight. This value varies mainly according to the fat content of the body; the fatter the individual the smaller is the total proportion of the body weight which is water. The extracellular phase constitutes about 15 to 20 per cent of the body weight, the exact magnitude depending on how this phase is defined and measured. By definition, that portion of the body fluid that lies outside the cell boundaries is extracellular. Experimentally, however, the functional cell boundary may differ from the anatomical cell boundary, the former varying according to which particular solute is being excluded. Consequently, it has become customary to refer to a given extracellular phase as a "space" occupied by the solute under discussion (e. g., chloride, sodium, thiocyanate, inulin). In terms of function the extracellular fluid phase may best be defined as that portion of the body fluid in which potassium exists in a low concentration. The experimental evidence upon which these concepts are founded is presented in detail in chapter 3.

The two fluid phases are sharply differentiated as to their electrolyte and protein composition (fig. 1-2). The principal ionic solutes of intracellular

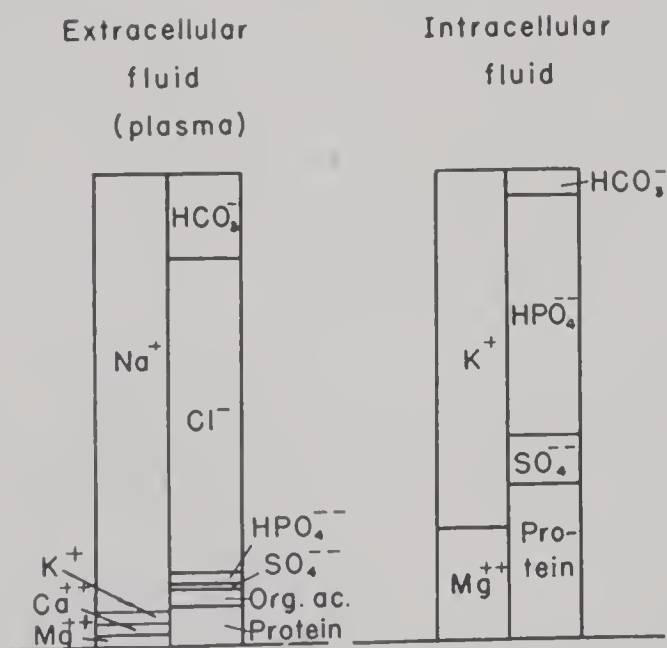


FIG. 1-2. ELECTROLYTIC COMPOSITION OF EXTRACELLULAR AND INTRACELLULAR FLUID

The positively charged ions, cations, are shown in the left-hand portion of each bicolumnar diagram, and the negatively charged ions, anions, in the right-hand portions.

In the extracellular fluid the principal cations and anions are sodium, bicarbonate, and chloride; in intracellular fluid they are potassium, magnesium, phosphate, and protein. The extracellular pattern shown is that of one of its subdivisions, plasma. Interstitial fluid differs in that it contains much less protein and therefore a higher concentration of all of the other ions. However the actual increase in the individual ions is modified by the Gibbs-Donnan effect.

fluid are potassium and magnesium as cations, and phosphate and protein as anions. In the extracellular fluid, sodium is the major cation and chloride and bicarbonate are the principal anions; a small amount of protein is present but is mostly in the portion restricted to the vascular system, the plasma. Water appears to be freely diffusible throughout the body, moving according to the dictates of the hydrostatic and osmotic pressures of the several phases. The distribution of water between extracellular and intracellular fluid depends on the factors that regulate in each phase the concentration of those solutes which are not freely diffusible. The dynamics of the movement of various fluid components within the body are discussed below.

The extracellular phase is further subdivided into at least three compartments: the plasma, the interstitial fluid, and the connective tissue. The first two of these subdivisions are differentiated by the high protein content of the plasma. They are not greatly different in their electrolyte composition since electrolytes and water are almost freely diffusible across the vascular wall. The ion concentrations on the two sides of the membrane differ only as required by the Gibbs-Donnan effect of the nondiffusible solute, protein. This involves a redistribution of solutes so that as an end result electrolytic and osmotic equilibria are established. At that point anions other than protein will be in lesser concentrations on the protein side of the membrane and in greater concentrations on the side opposite.

The distribution of water and electrolyte between the plasma and interstitial subphases of the extracellular fluid is determined by the relationship of hydrostatic pressures in the capillaries and tissues to the osmotic or oncotic pressures of the proteins in accordance with Starling's law (3b).

### *B. In Various Tissues and Organs*

Since individual tissues have specific functions, it is not surprising that they may differ in respect to their precise composition of water and electrolytes (fig. 1-3) (4a-c). Skeletal muscle represents the bulk of soft tissue in the body and for this reason usually is considered to be the model of body fluids as a whole. The liver differs in that its solid content varies over a much wider range, due to the deposition and mobilization of glycogen and fat. The skin contains a higher proportion of extracellular fluid. The erythrocyte differs in its sodium and potassium content. The cells of gastric mucosa, testes, and ovaries contain more chloride than do those of other tissues. Despite these individual differences, however, the proportions of solids, intracellular water, and extracellular water in the various tissues are similar enough to justify consideration of the fluids of the whole body as a single system. This simplification becomes mandatory when dealing with abnormalities created by disease states.



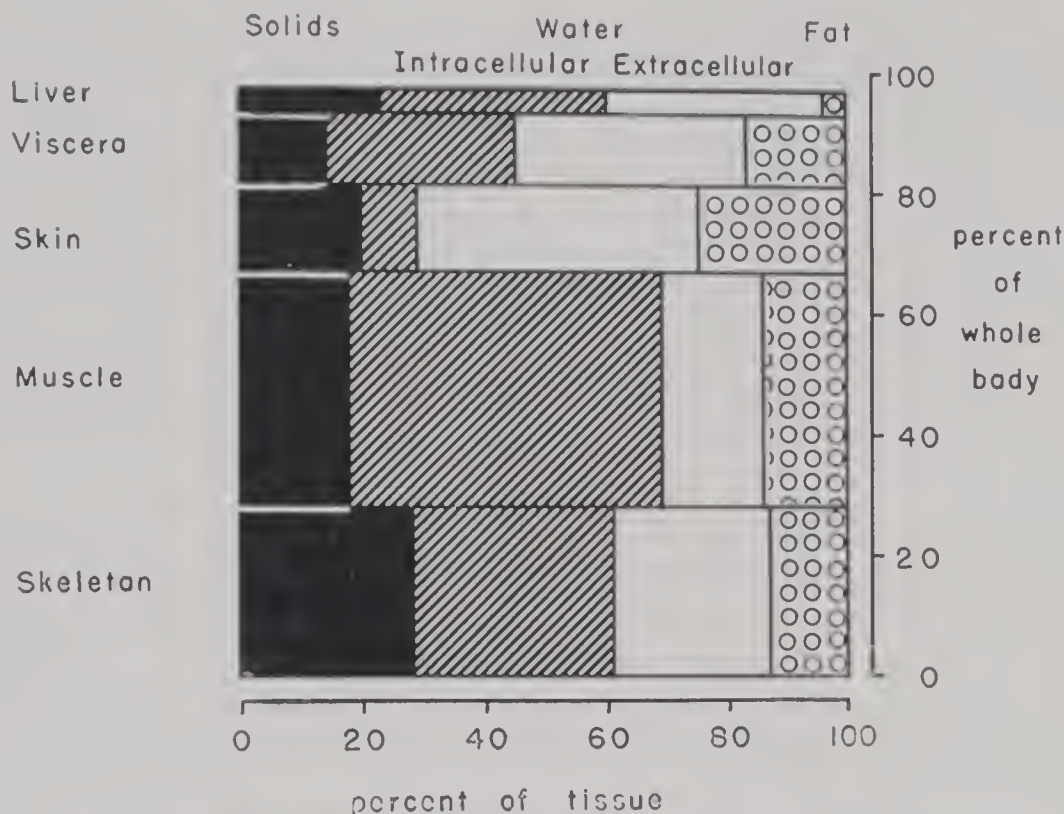


FIG. 1-3. RELATIVE PROPORTIONS OF SOLIDS, INTRACELLULAR AND EXTRACELLULAR WATER, AND FAT IN VARIOUS TISSUES OF THE DOG

From Harrison, Darrow and Yannet (1a)

### III. Internal Transfers of Fluid

#### A. Types of Movement of Fluid Components

The components of a solution or fluid, the solutes and the solvent, move along energy gradients that arise from the specific activity or chemical potential of the solvent (5a). These gradients produce four basic kinds of movement or transfers of fluid which together account for most, if not all, movements of fluid within the organism and the environment. These types of transfer are diffusion, osmosis, "active" transport, and mass-movement due to hydrostatic pressure.

**1. Diffusion along concentration gradients** is the simplest type of fluid movement and is illustrated in figure 1-4. When two phases or portions of a solution are differentiated only by a change in concentration produced as a result of the addition or subtraction of solute or solvent ( $H_2O$ ), the solutes and solvents diffuse in the direction of their respective lower concentrations, or along their gradients, until equilibrium is re-established. It should be remembered that the solvent has a concentration as well as the solute, i. e., from the standpoint of energy gradients a low concentration of solute, in relation to solvent, is a high concentration of solvent, in relation to solute. Therefore, solutes and solvents move along gradients which are

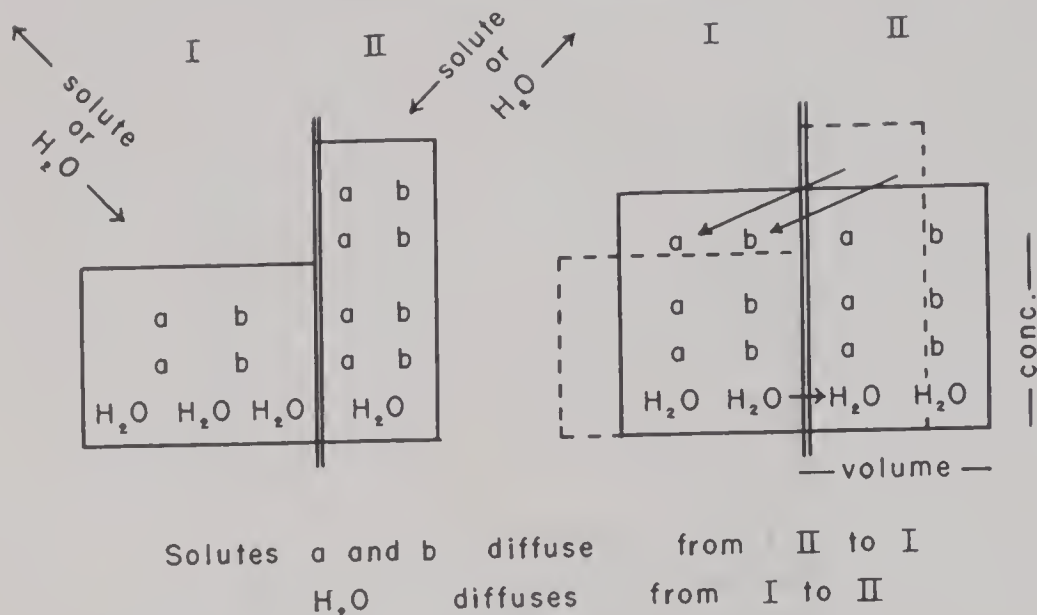


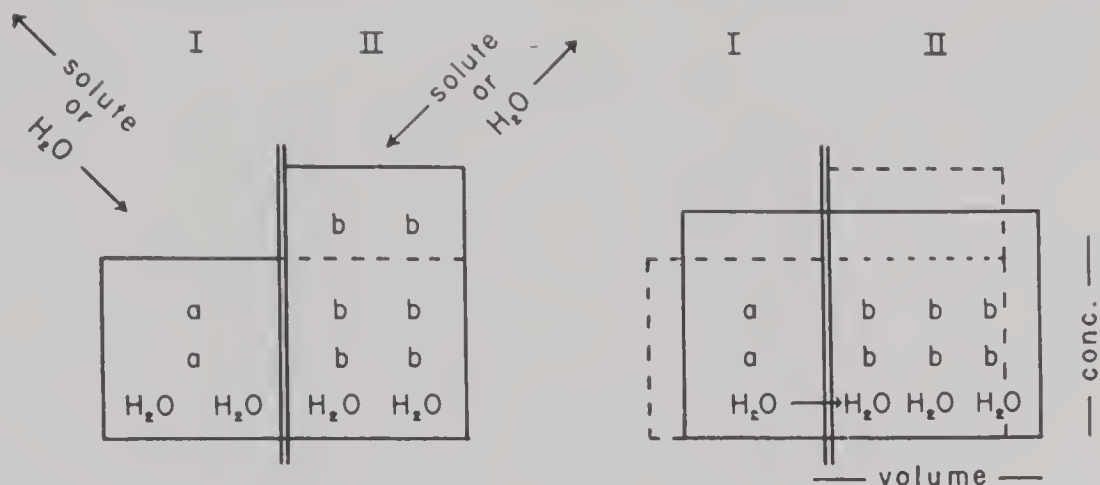
FIG. 1-4. DIFFUSION ALONG CONCENTRATION GRADIENTS

Phases I and II are differentiated only by inequalities in concentration produced by the addition or subtraction of solutes or solvent ( $H_2O$ ). Both solutes and solvent diffuse along their respective concentration gradients which are opposite in direction.

opposite in direction. The net result of these shifts of solute and solvent on the volumes of the respective phases will depend upon the relative rates or coefficients of diffusion of the solutes and solvents involved. The kinetic energy in the gradients is regarded as being derived from whatever process initially produced the change in concentration.

**2. Osmosis** is the transfer of fluid in response to osmotic pressure exerted by the restraint of a solute to one of two fluid phases. This is illustrated in figure 1-5. When two fluid phases are differentiated not only by inequalities in concentration of solutes and solvents, but also by the restraint or nontransferability of solutes and solvents, the solvent transfers between the two phases until the respective concentrations are equalized. The force exerted by this transfer of solvent is termed effective "osmotic pressure" and may be expressed in equivalent units of the hydrostatic pressure which it may oppose in a state of equilibrium. The energy in such an osmotic gradient is derived from the process that led to the change in concentration of the restrained solutes. This definition of osmosis holds irrespective of the nature of the restraint placed upon the solute, i.e., whether it is due to a semipermeable membrane or to an "active" process that continuously transfers a solute in one direction.

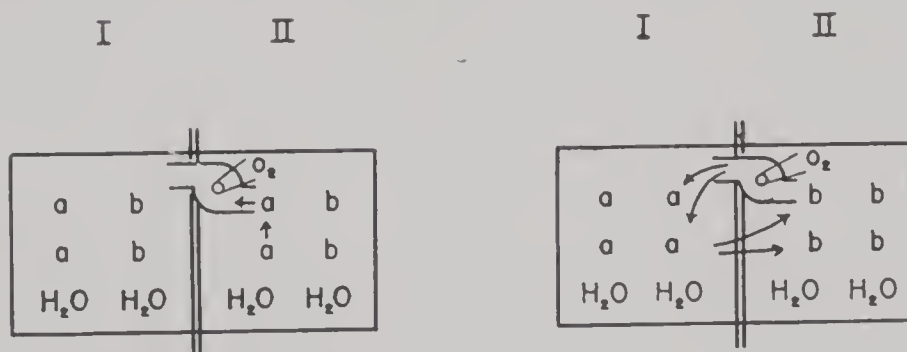
**3. "Active" transport** is the movement of a solute against a concentration gradient. Such a transfer is called "active" because it requires the expenditure of a further increment of energy at the site of transport. It is usually related to an oxidative metabolic reaction and is therefore represented in figure 1-6 as being transferred by a pump driven by oxygen. The



$H_2O$  transfers from I to II

FIG. 1-5. OSMOTIC TRANSFER OF FLUID

Phases I and II are differentiated not only by inequalities in concentration produced by the addition or subtraction of solutes or solvent ( $H_2O$ ), but also by the restraint of the solutes to their respective phases (a to I and b to II). The freely diffusible solvent ( $H_2O$ ) moves therefore from phase I with the higher concentration of solvent or the lower concentration of solute to phase II with the lower concentration of solvent and the higher concentration of solute, until the concentrations are equalized.



Solute a actively transferred from II to I  
solute b diffuses from I to II

FIG. 1-6. "ACTIVE" TRANSFER OF FLUID

Phases I and II are differentiated by the active transfer of a solute from one to the other phase against a concentration gradient, i.e. solute a from phase II to phase I. The transfer is active in that it requires energy that is usually derived from an oxidative metabolic reaction and hence is represented by a pump driven by oxygen. The effect of the transfer is to cause a diffusion of other solutes in the opposite direction or to set up an osmotic gradient.

result of such a process on the other constituents of the two fluid phases depends upon their diffusibility. If other solutes are freely diffusible, they will simply diffuse in the direction opposite to that of the actively transported solute. If not, an osmotic gradient is established with a resultant shift of solvent as in figure 1-5.



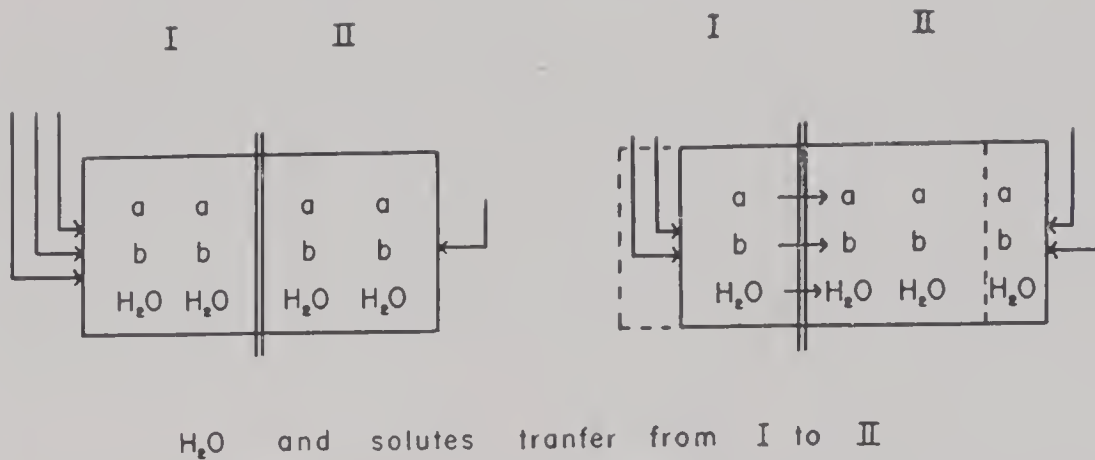


FIG. 1-7. MASS MOVEMENT OF FLUID DUE TO HYDROSTATIC PRESSURE

Phases I and II are differentiated only by difference in hydrostatic pressure as indicated by the number and height of the arrows. Solutes *a* and *b* and the solvent (H<sub>2</sub>O) move along the hydrostatic pressure gradient until the pressures of the two phases are equalized.

**4. Mass-movement of fluid due to hydrostatic pressure** gradient is illustrated in figure 1-7. Where two portions or phases of a solution are differentiated, *not* by differences in concentration or transferability of solute or solvent but by hydrostatic pressure, all constituents of the fluid move together from one phase to the other phase along the pressure gradient until the pressures are equalized. The energy in this system is derived from the process that sets up the hydrostatic pressure gradient.

**5. Flux and turnover** must be distinguished from diffusion, osmosis, active transfer and mass-movement due to hydrostatic pressure. Flux is the rate of movement in one direction of an individual ion or molecule, solute or solvent, between two phases by any one of the three types of movement described above (diffusion, osmosis, or active transfer). Ions or molecules of the same fluid component may be simultaneously moving in opposite directions to each other. If the flux in one direction exceeds the flux in the other direction there is a net transfer or a *net flux* in that direction. If the flux in each direction is exactly the same, there is no net transfer or net flux; in these circumstances the rate of turnover may be high while the net transfer is zero. Turnover may be defined as the absolute sum of the flux in both directions.

#### *B. Integration of These Basic Types of Fluid Transfer in the Three-Phase System of Plasma: Interstitial Fluid: Intracellular Fluid*

**1. Plasma: interstitial fluid.** As indicated previously, the maintenance of the plasma volume, or the distribution of fluid between the two subdivisions of extracellular fluid, is the result of a balance between capillary hydrostatic pressure and the osmotic pressure of the plasma proteins which are almost entirely within the plasma side of the capillaries. This is

the well-known *Starling's Equilibrium* (3b). These two major forces of fluid transfer are modified to some extent by the osmotic pressure of the small amount of protein in the interstitial fluid and by the hydrostatic pressure in this compartment resulting from the elasticity of tissues, visceral capsules, and skin. These hydrodynamic factors, as indicated in figure 1-8, a, determine the net volume flow (or net flux or mass-movement) of fluid across the capillary membrane. Normally such net flux is relatively slow, amounting to about two per cent of the plasma flow, compared to the

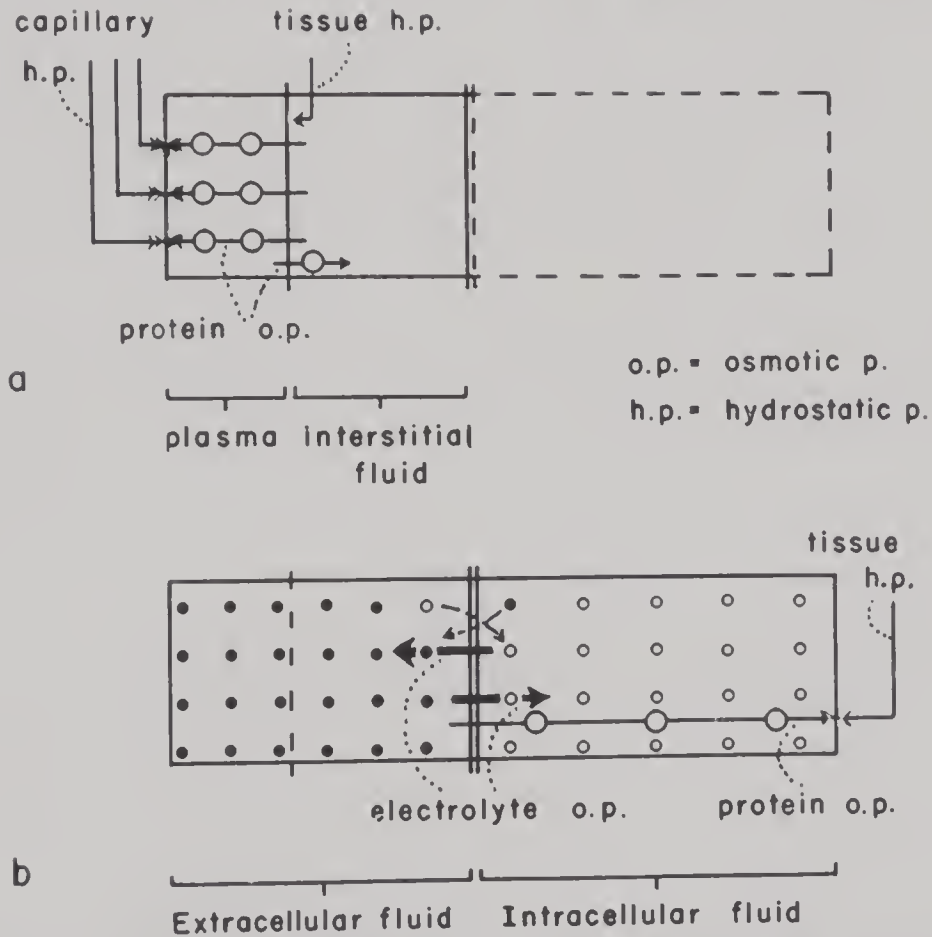


FIG. 1-8. DIAGRAM OF FORCES THAT DETERMINE THE DISTRIBUTION OF FLUID: (a) BETWEEN PLASMA AND INTERSTITIAL SPACES, AND (b) BETWEEN EXTRACELLULAR AND INTRACELLULAR PHASES

Hydrostatic pressures are indicated by the angulated arrows outside the phases of fluid; osmotic pressures by the horizontal arrows within. Large open circles represent protein solutes restricted to the several phases. Small open and solid circles represent ionic solutes such as electrolytes restricted to the intracellular and extracellular phases respectively by a process of active transfer requiring energy and exerting an osmotic pressure accordingly.

The distribution of fluid between the intravascular plasma and the extravascular interstitial fluid in *a* is determined by the relationship of the hydrostatic and oncotic or protein osmotic pressures according to the Starling hypothesis.

In *b* the fluid is distributed between the extracellular and intracellular phases mainly according to the osmotic pressures resulting from the active differential distribution of electrolytes.

total flux or turnover of small molecular solutes in each direction. These substances, water, electrolytes, and crystalloids such as urea and glucose, diffuse rapidly back and forth at flux rates that range from 10 to 80 times their flow rates in plasma. Diffusion is not unrestricted. The rate depends upon the ratio of the restricted diffusion coefficient to the rate of net volume flow. Nevertheless, for the small molecular substance little "sieving" effect with creation of concentration gradients takes place at physiological rates of volume flow or net flux. Such is not the case for the large molecules of protein whose restriction is great at such rates of volume flow. It is only when the latter falls off and filtration is slowed that the diffusion of protein across the capillary membrane becomes significantly increased. In these circumstances, e.g., shock, the protein content of interstitial fluid may rapidly rise. These concepts of exchanges between the two phases have recently been thus defined by Pappenheimer (5b).

**2. Interstitial fluid: intracellular fluid.** The distribution of fluid between these two phases depends primarily upon the osmotic pressure of the dissociated ions or electrolytes and other solutes in the respective phases (figure 1-8, b). This osmotic pressure is the product of a series of factors that include active transport of solutes across the cell barrier, consequent diffusion of other solutes, and production, modification, or synthesis of certain anions (phosphates and proteins) within the cell that are restrained to the intracellular phase by their size. The energy for active transport and for the synthesis of the large anions comes from the oxidative reactions of metabolism. In addition to osmotic pressure of the solutes, electrolytes and proteins, there must also be a hydrostatic pressure that tends to limit the passage of fluid into the intracellular phase. The integration of these forces in the three-phase system is illustrated in figure 1-9.

**3. An "open system."** This three-phase system is open at both ends, as indicated by the broken arrows in figure 1-9. It is this fact that makes it a dynamic rather than a static system, and so modifies the application of the second law of thermodynamics. It is usually appreciated that the system is open at the plasma end where exchanges constantly occur between the organism and the external environment. It is less often recognized that, to a limited extent, the system is also open on the cellular end, at least with respect to the forces that effect transfers of water. Since the production of energy for active transport and changes in the number of molecular aggregates, and therefore in osmotic activity, as well as the synthesis of water and other solutes, all take place within the cell, it is clear that the fluid dynamics of the system can be altered at this end. This is clinically significant in that the fluid balance of the body can be altered by metabolic events in the peripheral tissues as well as by events in the organs of exchange with the outside world.



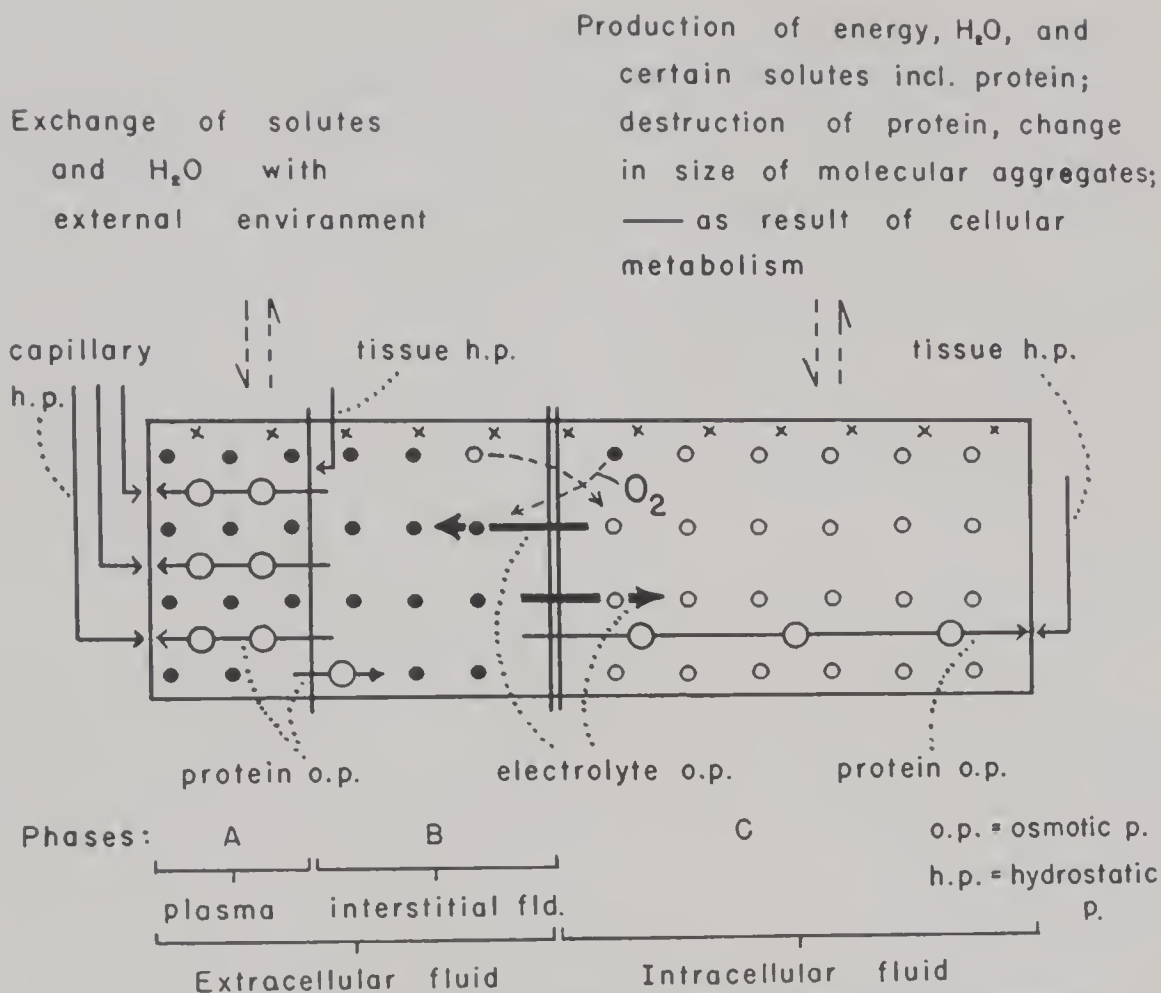


FIG. 1-9. DIAGRAM OF THE FOUR MECHANISMS OF FLUID TRANSFER AS INTEGRATED IN THE THREE-PHASE SYSTEM, PLASMA:INTERSTITIAL FLUID:INTRACELLULAR FLUID

Symbols are as in the preceding figure. Crosses (x) represent solutes that are freely diffusible throughout all three phases and therefore exert no differential osmotic pressure.

The broken reaction arrows above the plasma and above the intracellular fluid indicate that, with respect to forces that effect movements of fluid, the system is open at both ends.

**4. The differential distribution of ions between cells and extracellular fluid.** The differential distribution of ions which is predominantly characterized by sodium being outside and potassium being inside cells, is a basic characteristic of the dynamics of the body fluids. Many theoretical explanations have been advanced. In general they may be divided into two categories: a) those based on passive physico-chemical forces, and b) those that involve the active expenditure of energy.

In the former category lies the older concept of the cell boundary as an inert semipermeable membrane through which substances do or do not pass depending on their size. A major difficulty with this concept lay in the question of how the intracellular constituents such as potassium get there in the first place. The demonstration (6a-d) that potassium readily crosses



the cell boundary in a constant state of flux, completely invalidated the simple concept of the inert semipermeable membrane. Boyle and Conway (6e) attempted to circumvent this difficulty by suggesting that the membrane is permeable to potassium but impermeable to sodium because of the difference in diameter of the two hydrated ions. Since the larger size of the cellular anions, protein and phosphate, restricts them to an intracellular position, the only cation able to pass through the phase barrier, potassium, diffuses into the cell to maintain electro-neutrality, and the cation sodium remains behind with chloride as the principal extracellular anion.

Boyle and Conway's theory, however, ran aground on the clear-cut evidence that sodium does enter many cells, especially those of skeletal muscle (6f-j). Dean (6k) pointed out this difficulty and suggested that sodium is free to diffuse into the cell but is actively transported outward by a "sodium pump," thus invoking the expenditure of energy to maintain the differential ionic distribution. Conway (6l, m) has proposed a redox pump, i.e., an oxidation-reduction system for the active transport of sodium across the membrane which is similar to the active transport of sodium across the frog skin described by Ussing (6n). Such active transport might involve a carrier enzyme in the membrane that takes up an electron from a neutral intracellular molecule, permitting dissociation and diffusion of the cation outward. The electron is then returned on the negatively charged carrier to repeat the cycle. The Conway system and redox pump are represented diagrammatically in figure 1-10.

Recently, Ling (6o) has attempted to explain more completely differential ion distribution on a purely physico-chemical basis. He hypothesizes that the separation of sodium and potassium by fixed negative charges on the proteins takes place throughout the whole cell and not at the cell boundary, i. e., there is no "membrane." This he believes to be due to the fact that the dielectric constant of the water between the protein anion and the cations is lower the smaller the diameter of the hydrated cation. Because the diameter of the hydrated ion of potassium is less than that of hydrated sodium, the former is attracted and the latter is rejected. Nevertheless, since metabolic processes condition the quantity and spatial arrangement of the protein negative charges, they must have an indirect effect on the differential distribution of sodium and potassium.

Potassium is known to be intimately associated with cellular phosphorylation and the glycolytic cycle. Its uptake by muscle may occur with the action of insulin (7a) and it is essential for the formation of adenosine triphosphate (7b, c). Its movement into and out of cells has been shown to be affected by a wide variety of metabolic inhibitors and stimulants (8a-d). It appears difficult, therefore, to explain this basic phenomenon without

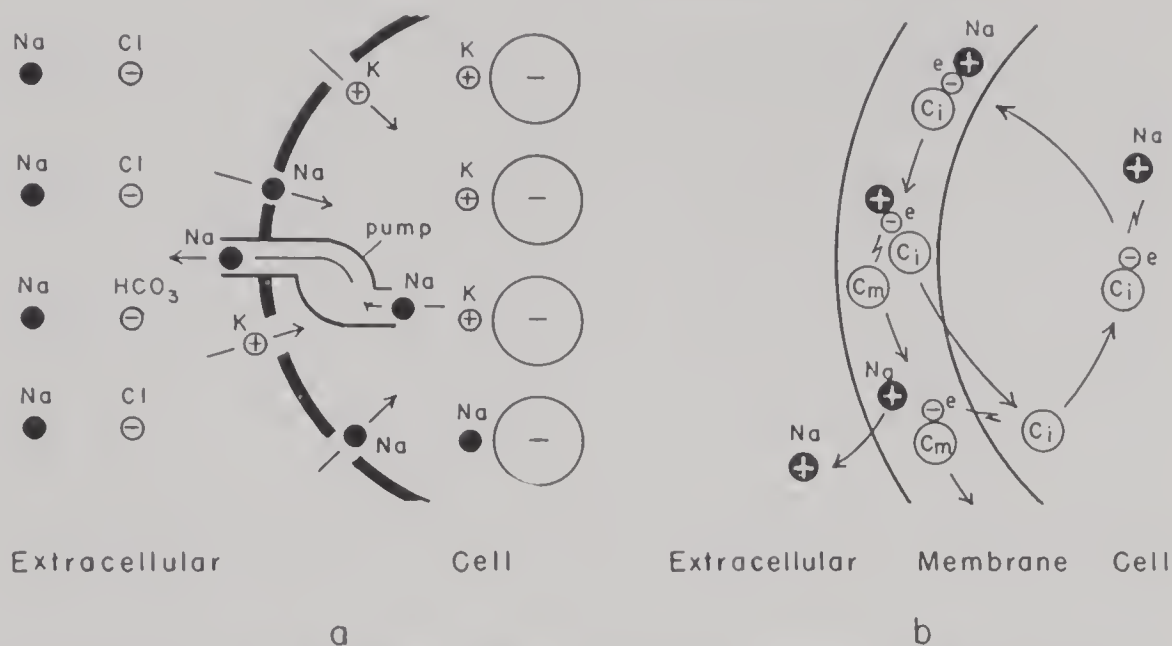


FIG. 1-10. THE CONWAY THEORY OF THE DIFFERENTIAL DISTRIBUTION OF CATIONS AND ANIONS BETWEEN EXTRACELLULAR FLUID AND CELLS

In *a* the cell boundary is depicted as a membrane permeable to small ions such as sodium, potassium and chloride but impermeable to the larger intracellular anions consisting of proteins and phosphates. Since sodium is "actively" transported outward by an energy-driven pump (redox), potassium is distributed primarily in cells to maintain electroneutrality.

In *b* the details are presented of an oxidation-reduction system for the active transport of sodium ion through the cell membrane, as proposed by Conway (6l, m) and by Ussing (6n). An intracellular carrier enzyme (C<sub>i</sub>) negatively charged with an electron (e<sup>-</sup>) carries the positively charged sodium to the membrane. Here a neutral membrane carrier (C<sub>m</sub>) gains the electron and so transports the sodium ion to the outer surface where dissociation frees it into the extracellular fluid. Subsequently, the neutralized intracellular carrier gains back the electron from the membrane carrier and so is ready to repeat the cycle.

invoking the utilization of energy. For a complete discussion of this complex problem the reader is referred to a series of reviews (6k-n, 9a-f).

### *C. The Cardiovascular System and Internal Transfers of Fluid*

Our concept of the body fluids, however, must go beyond the three-phase system just outlined. In the mammalian organism this three-phase system exists in many different tissues and organs which are widely separated from one another. These spatially separated units of body fluid are connected only by the extended lines of communication of the cardiovascular system. It is an oversimplification, therefore, to consider the body fluids as single solutions contained, so to speak, in a beaker (figure 1-1). The multicompartmental character of the body fluids is more accurately diagrammed as in figure 1-11. Here is emphasized the role of the circulation as the "mixing apparatus." The several phases of body fluid are homogeneous in composition only insofar as the circulation is competent.

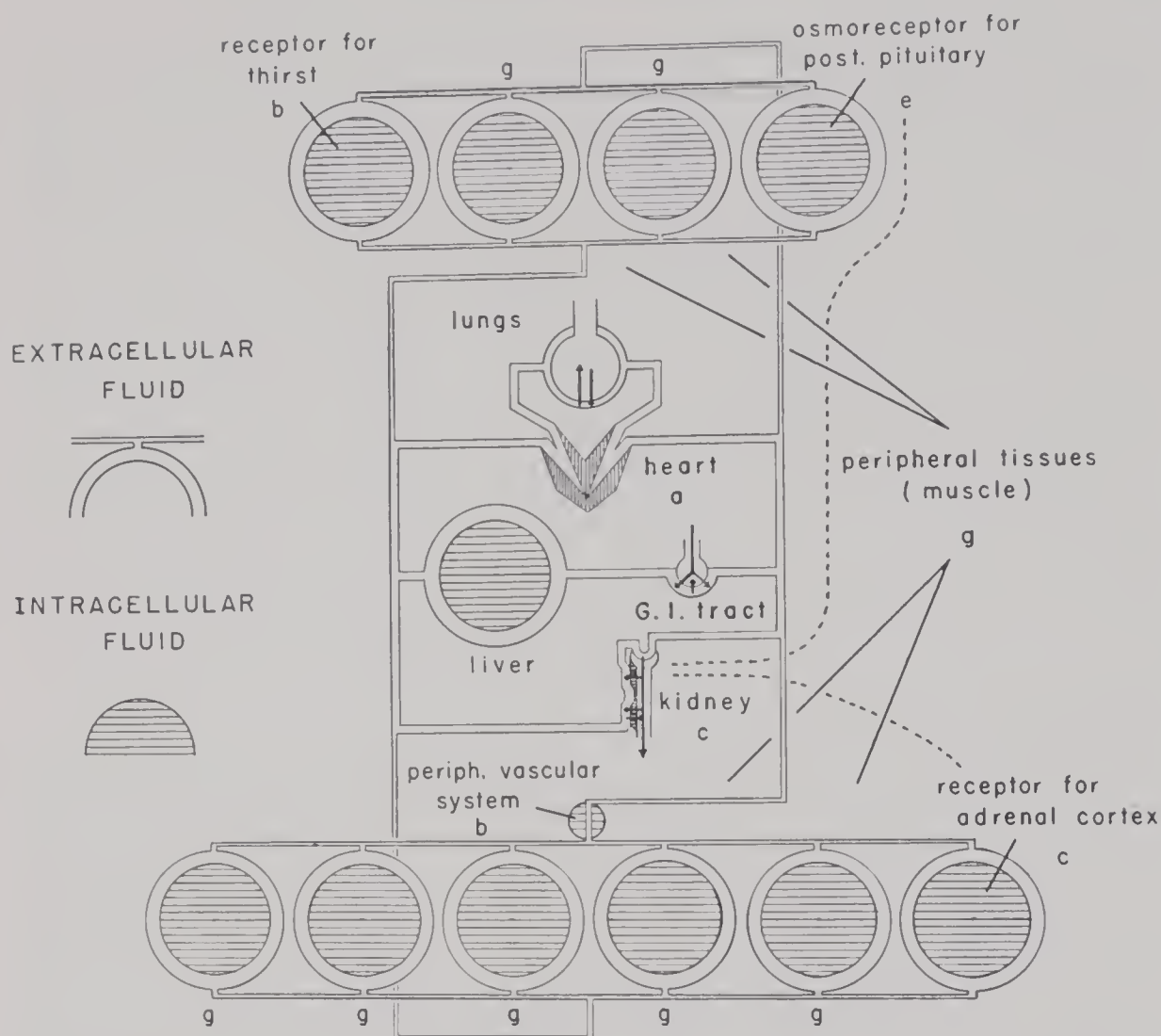


FIG. 1-11. DIAGRAM OF THE INTRACELLULAR AND EXTRACELLULAR FLUIDS OF THE BODY, INCLUDING THE PATHWAYS OF INTERNAL CIRCULATION AND THE SITES OF TRANSFERS WITH THE EXTERNAL ENVIRONMENT

The multicompartmental character of the body fluids is emphasized as well as the role of the circulation as the "mixing apparatus" for the extracellular fluid. Fluid transfers of the four basic types between the fluid phases as diagrammatically shown in figure 1-10, involving the various fluid constituents, take place in each of the many units of the body fluids. Loci of some of the intracellular fluids in which changes in composition may affect, directly or indirectly, the distribution of fluids in the body as a whole are indicated by letters *a* to *g* inclusive. (From Elkinton and Squires (10a).)

In each unit of this multicompartmental system, the four integrated types of fluid transfers, shown in figure 1-9, are taking place. These transfers are not only integrated in each unit but also interrelated throughout the larger system. The hydrostatic pressure gradients in capillaries are maintained by the central force or pump, the heart, and by the various factors that enter into peripheral vascular resistance. Diffusion and osmotic gradients set up by exchanges between the plasma and external environment are initiated by certain organs. The effects of these gradients are transmitted to the rest of the organism through the circulation (10a). This



tendency of a solute to spread throughout the body fluids has been termed "fugacity" by Wolf (10b). Such a transfer, however, is compounded of the four basic types, outlined above, working in this multi-unit system. Thus the exchanges between the body fluids and the environment are entirely dependent on the adequacy of the circulation. Oxygen and foodstuffs can only be supplied to the cells from the lungs and gastrointestinal tract by transport through the circulation. Metabolic end products as well as components of the body fluids in the peripheral tissues can only be excreted through lungs, skin, gastrointestinal tract, and kidneys by transport through the circulation and through that portion of blood which circulates through those particular organs. The circulation, therefore, is an integral part of the body fluid dynamics with respect to both internal and external transfers.

#### IV. Exchanges between the Body Fluids and the External Environment

##### A. *Organs of Exchange*

The four organs in which these exchanges take place are illustrated in figure 1-11.

**1. The gastrointestinal tract** is normally the sole route of entry from the external environment of nutritive substances and of the constituents of the body fluids. It is the route of egress of unabsorbed solids from food, of the products of bacterial metabolism in the gut, of the excretory products of the liver, and of a major portion of calcium, magnesium, and phosphorus. Some potassium is present in the normal stool but there is almost no sodium or chloride and relatively little water.

Exchanges of electrolyte and water take place primarily in the stomach and small intestine. Large amounts of extracellular water with varying ionic patterns are transferred from plasma into the lumen of the stomach and small intestine and are reabsorbed again. This fluid in the stomach is more acid if it comes from the parietal cells and is more alkaline, i.e., contains less hydrogen ion, if it comes from the cells of the fundus. In the small intestine the fluid secreted, *succus entericus*, becomes progressively more alkaline as bicarbonate displaces chloride. The volumes of these fluid exchanges are large, amounting to many liters turned over in 24 hours (2d). Hence, any disruption of the normal anatomy or activity of the gut that leads to external loss of these fluids results in rapid depletion of important constituents of the extracellular fluid.

The factors that control the exchanges of fluid between plasma and gut are not completely known. The secretion of hydrochloric acid in the stomach is complex and involves a hydrogen ion exchange in which carbonic anhydrase may be involved (11a). In the small intestine regulation of fluid



transfer has been postulated to depend on variations in the relation of osmotic and hydrostatic pressures in the fluids of the lacteals and gut lumen, respectively (11b). A more complex exchange mechanism of water and electrolytes has been suggested by Visscher (12a-d) and there is no doubt that the cells of the intestinal wall transport these substances differentially. The progressive rise throughout the intestine of the ratio of potassium to sodium and to water, reaching a mean potassium:sodium ratio of about 5.0 in the normal stool (12e, f), clearly indicates these differential exchanges. Some evidence has been brought forward to indicate that adrenocortical insufficiency and adrenocortical steroids may modify the exchange of sodium across the intestinal wall (12g-l). Care must be taken, however, not to draw too close an analogy between the cells of the intestinal mucosa and those of the renal tubule, since the former show little facultative ability to modify their exchanges in response to changes in the composition and volume of the fluids of the body as a whole.

**2. The lungs**, with respect to structural constituents of the body fluids, are entirely an excretory organ. Carbon dioxide is eliminated at a rate that is regulated by its partial pressure in the alveoli, constituting the respiratory fraction of acid-base regulation. The alveolar partial pressure is regulated by the complex respiratory mechanism to accomplish the excretion of metabolically produced carbon dioxide at a basal rate of some 13,000 millimols per day, an order of magnitude of daily net turnover far in excess of the other constituents of the body fluids (see table 23-I). Water vapor is lost continuously through the lungs, accounting for some 25 per cent of heat lost from the body (13a). This water loss is an obligatory function of caloric expenditure and continues with relatively little decrease in rate in the face of severe dehydration (13b). Although this water loss is insensible, as is that vaporized from the surface of the skin (see below), these two routes of insensible water loss may amount to 800 to 1500 milliliters of water per day in the nonfebrile adult and must be taken into account in maintaining the water balance of any patient.

**3. The skin** is likewise a site of transfer to the external environment of certain constituents of body fluids. Water is vaporized from the skin in a continuous manner as it is from the pulmonary alveoli. This fluid loss, like that from the lungs, bears an obligatory relation to caloric expenditure (13a). When for reasons of increased production of heat, as in fever or muscular exercise, or of increased environmental temperature more heat must be expended, the mechanism of sweat comes into play. This is a secretory activity and results in the loss to the body of sodium, chloride, and potassium, as well as of water. The concentration of these solutes in sweat is hypotonic with respect to extracellular fluid, that is, more water than salt is lost. The precise concentration of these solutes is influenced by a variety

of factors, including rate of flow and acclimatization, and by hormones (14a-k). There is clear evidence that adrenocortical steroids act upon the tubular cells of the sweat gland as upon those of the kidney, inhibiting the excretion of sodium and chloride and enhancing that of potassium. Despite the many factors that influence the amount and composition of fluid transfers through the sweat glands, they are relatively insensitive to homeostatic needs and respond primarily to the dictates of the heat transfers of the body.

**4. The kidney** is the chief organ of regulation of the body fluids. The exchanges by which this regulation is effected are extremely complex and are still the subject of extensive investigation. For many substances of the body, especially end products of metabolism, the kidney is an organ of excretion or egress to the external environment. For the main structural constituents of the body fluids, however, the kidney is primarily an organ of regulation. The kidney regulates not only their concentration in relation to one another, i. e., water to electrolytes, cations to anions, cations to cations, and anions to anions, but also the total amounts of these constituents. This complex regulation is accomplished by the interplay of *a*) the intrarenal processes of glomerular filtration, tubular reabsorption, and tubular secretion, *b*) the circulation between the rest of the body and kidneys, and *c*) the nervous and hormonal influences that receptors at a distance bring to play on the kidney and on the circulation.

Only certain basic phenomena of this regulatory mechanism will be outlined here. For a detailed discussion of the modern concepts of renal physiology the reader is referred elsewhere (10b, 15a-c). The intrarenal processes, as stated above, begin with the formation in the glomeruli of an ultrafiltrate of plasma. This glomerular filtrate, which approximates in a normal adult the enormous volume of about 180 liters per day, is modified as it passes through the renal tubules. This modification consists of reabsorption of various constituents from tubular filtrate or urine to plasma, and by secretion and transfer by the tubular cells of certain constituents from plasma to urine. The urine that arrives in the renal pelvis and bladder is the net resultant of these three processes. Since an average normal urinary output is about 1.5 liters per day, it is obvious that most of the glomerular filtrate is reabsorbed during its passage through the tubules. Thus about 99 per cent of the filtered water, sodium, and chloride is reabsorbed and only about one per cent is excreted. Homeostatic regulation of these principal constituents of extracellular fluid therefore lies in the relationship of the quantities filtered to the quantities reabsorbed. In disease states alteration of either filtration or tubular function, or both, may disturb this relationship and its regulatory process. If the abnormal alteration of one of these functions cannot be compensated for by the other, a state of glomerulo-tubular imbalance obtains. Thus marked reduction of the rate of glomerular filtra-



tion may contribute to sodium and water retention as the tubules reabsorb a greater proportion of these substances from the filtrate, as in some types of circulatory failure. Or, tubular damage may lead to deficits of sodium, potassium, and water by virtue of impaired reabsorption of glomerular filtrate, as in the healing phase of acute renal failure due to tubular necrosis.

In the normal organism, these processes are subject to very precise adjustments, which are effected primarily through regulation of tubular transfers. Not all of these regulatory mechanisms are known but some of them are humoral. The tubular reabsorption of sodium and of chloride is augmented by certain steroids of the adrenal cortex, while that of water is enhanced by the antidiuretic hormone of the posterior pituitary gland. Thus, while there may be obligatory reabsorption of some 80 to 85 per cent of water and salt in the proximal and thin segments of the renal tubule, the remaining 15 to 20 per cent is subject to facultative reabsorption in the distal tubule and possibly the collecting ducts. The disease entities, Addison's disease and diabetes insipidus, which ensue when the functions of these respective endocrine glands are insufficient, are characterized by abnormalities of renal regulation of sodium and water excretion. The degree to which these endocrine systems enter into normal physiological regulation and the mode of stimulation of their receptor organs have been only partially defined.

The regulation of production of antidiuretic hormone by the posterior pituitary gland depends at least in part on certain receptor cells in the hypothalamus. These receptors have been shown experimentally by Verney (15d, e) to be extremely sensitive to variations in the total osmolar concentration of certain solutes in the extracellular fluid that bathes them as well as to stimuli of other kinds such as emotion, pain, nicotine, and alcohol. Stimulation of these *osmoreceptors* of Verney by hypertonic solutions of sodium chloride resulted in an outpouring of antidiuretic hormone and of inhibition of a standard water diuresis. This mechanism would appear to provide for the physiologic or homeostatic regulation of water excretion by the kidney. These receptors are represented diagrammatically in figure 1-11.

Adrenocortical regulation of tubular transfers of sodium probably occurs but the receptor mechanism is not known. In animals this gland can be stimulated by discharges of the autonomic nervous system resulting in epinephrine release and production of adrenocorticotrophin as well as perhaps by more direct stimulation of the anterior pituitary by the central nervous system. Aldosterone, an endogenous adrenocortical steroid, which is many-fold more potent than the synthetic desoxycorticosterone in its effect on tubular transfers of electrolytes, has recently been isolated by Reichstein (16a) (see chapter 5). This is probably the natural hormone on

the efferent end of this regulatory pathway. However, the receptor organs (fig. 1-11) and the variable or variables in the body fluids that signal the need to retain or to excrete sodium, are still the subject of investigation. Obviously, the excretion of water and the excretion of sodium are closely integrated. This is true despite the fact that antidiuretic hormone appears to have no direct effect on the tubular transport of sodium, and desoxycorticosterone no direct effect on the tubular reabsorption of water. Adrenocortical 11-oxysteroids such as cortisone or hydrocortisone influence the renal tubules and so affect the tubular reabsorption of water as well as that of salt (16b). Entirely aside from humoral influences on tubular transfers, the conditioning of the excretion of water by that of sodium, and *vice versa*, occurs within the kidney under extremes of loading of one or the other. Prerenal conditioning is the more likely mechanism of precise regulation and must operate through the receptors such as those mentioned above. Such regulation of the volume of the body fluids is discussed below.

The regulatory action of the kidney on the structure of the body fluids is not confined to water and total extracellular electrolyte or sodium. It shares with the lungs the maintenance of the acid-base equilibrium of the body by physiologic processes that have recently been elucidated in detail by several groups of investigators including Pitts, Gilman, Berliner, and their associates (17a-e, 15c). Under conditions of alkali excess when the body needs to dispose of cations, bicarbonate ion is excreted in an alkaline urine. In acid or anion excess, a number of interrelated renal mechanisms come into play. Hydrogen ion, secreted by the renal tubule, exchanges for bicarbonate-bound sodium and potassium in the glomerular filtrate, as well as with one cation of the dibasic phosphate. The result is reabsorption of the sodium and potassium and the excretion of an acid urine. The hydrogen ion in the tubule is dissociated from carbonic acid which is formed from carbon dioxide and water in the tubular cell under the enzymatic stimulus of carbonic anhydrase. This reaction is conditioned by the carbon dioxide pressure and pH of the body fluid, and so constitutes a finely adjusted renal mechanism for the regulation of acid-base equilibrium. Fixed cations of the body, sodium, potassium, calcium, and magnesium, are further spared by the renal tubular production of ammonium ion. Since potassium is involved as well as sodium in the renal ion exchange mechanism, under some circumstances potassium secretion bearing a reciprocal relation to hydrogen secretion, it is apparent that intracellular electrolytes take part in the total body response to acid-base stress. For a detailed discussion of these linked exchanges and their relation to cellular transfers the reader is referred to chapters 10 and 11.

This brief summary of the renal regulation of body fluids outlines some



of the processes by which the kidney controls the quantities in the body of the various constituents of the body fluids as related to the total solvent, water, of the various fluid phases, and as related to each other.

### *B. Volume Regulation and Homeostasis*

**1. Regulation of volume of the body fluids.** Renal adjustments of one constituent of the body fluids in relation to another, as outlined above, are more readily understood than are those of the total volume of the several phases of body fluid. This paradox is exemplified by the much greater rapidity of excretion of either water or salt when given separately rather than as isotonic saline solution. Nevertheless the kidney participates in the regulation of volume as well as the composition of body fluids, and these regulatory mechanisms are the subject of much current investigation.

The evidence for separate mechanisms of volume regulation has been adduced in a variety of ways. The renal excretion of water and electrolytes has been shown to be conditioned by variations in the body fluids remote from the kidneys. These variables have included cellular hydration, plasma, interstitial, and total extracellular fluid volume, intracranial volume or blood flow, and cardiac output. Changes in cellular hydration induced by water deprivation and by hypertonic solutions have been found to be associated with changes in the rate of excretion of sodium, changes that are opposite in direction to those predicted from the alterations in concentrations of the ion in plasma. Changes induced in plasma volume independently of interstitial volume may affect sodium excretion. Intracranial distension by cuffs around the neck or by recumbency may vary the rate of sodium excretion. However, since head down tilting reverses the effect of recumbency, the intracranial variables must be more than pressure or volume changes, perhaps blood flow. Intrathoracic pressure changes and venous distention of various peripheral areas of the body have been shown to influence the rate of sodium excretion by the kidney. Since all of these variables have been found to operate independently of measurable changes in renal dynamics or plasma concentration, the conclusion is forced that some other regulatory mechanisms are operative that involve receptor areas outside the kidneys. The means by which these receptors effect changes in renal function are likewise unknown, (18a-k). Humoral agents are involved, such as antidiuretic hormone and adrenocortical hormones, although recent evidence indicates that the latter hormones are not necessarily or always operative and that neural control of the kidney may be a significant factor (18l, m). Disturbances in the central nervous system have been found to be associated with abnormalities in sodium balance (18n-p) which strongly suggests a disturbance in receptors and pathways that regulate intake and output of solutes

and water. Whatever may be the afferent and efferent stimuli of these receptors, there can be no doubt of their existence and in figure 1-11 at least one more receptor should be added for volume.

It must be recognized that the thirst mechanism is an integral part of the dynamics of the fluid balance of the body. Intake of water must be related to output. It has been shown that alterations in various dimensions of the body fluids, as in sodium depletion or in certain stages of congestive heart failure (19a-d), may alter the normal response of the thirst mechanism and its relation to antidiuretic hormone production. Finally, the peripheral tissues themselves, figure 1-11, may directly affect localized movements of water in those tissues by changes in intracellular osmotic activity dependent on alterations in cell metabolism. Although these are purely internal fluid transfers, they may affect the exchanges between the organism and the external environment.

**2. Thermodynamic and regulatory concepts.** As we conclude our consideration of body fluid dynamics, it is clear that one of the prime characteristics of the body fluids and the organism as a whole is the ability for self-regulation to the end that a steady state is maintained. For this characteristic, perhaps first formulated by Claude Bernard (3a), Cannon (20a) coined the term *homeostasis*. Homeostasis comprises many and various dynamic processes at the cell, organ, and whole body level, described and undescribed.

The concept of self-regulation, long familiar to physiologists, has recently been the center of renewed interest in the field of cybernetics or the science of communication. This field has developed as the need has grown for regulatory devices in mechanical and industrial processes and as the science of electronics has vastly improved the techniques of communication. The writings of Wiener and others provide source material on the subject (20b-d). From cybernetics the physiologist may borrow to his advantage vocabulary as well as concepts.

In figure 1-12 is shown the schema of a self-regulating mechanism. The input (A) directly affects the output (B); the output (B) in turn automatically adjusts input (A) by means of a servomechanism that consists of a reverse signal or *feed-back* amplified, if necessary, at (C). The *feed-back* is termed *negative*, in the cybernetic vocabulary, because it tends to cancel an initial error in performance. This schema can be used equally well to represent a revolving shaft with a governor, an automatically controlled industrial plant for the production of chemicals, or the intake and excretion of water by the human body.

A basic characteristic of any self-regulating mechanism is oscillation of performance. This is illustrated in figure 1-13 in which three types of oscillations are shown. When the negative feed-back just cancels the error of

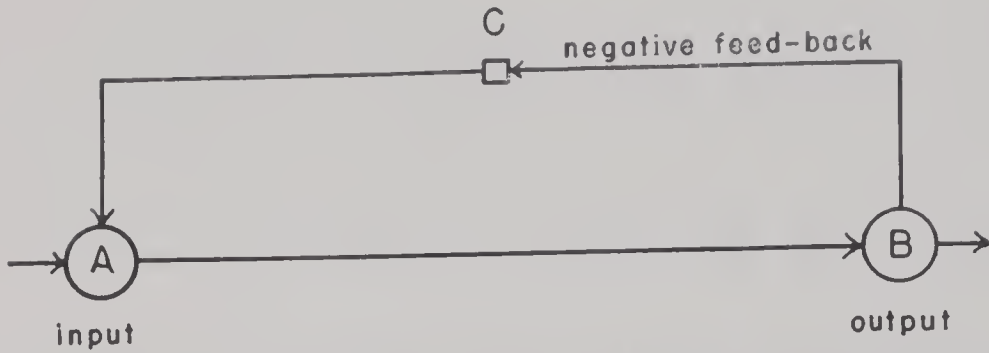


FIG. 1-12. SCHEMATIC REPRESENTATION OF AN AUTOMATIC SELF-REGULATING OR "SERVO" MECHANISM

Input (A) conditions directly output (B); output (B) in turn automatically adjusts input (A) by means of a servo-mechanism consisting of a reverse signal, or feed-back, amplified at C. The feed-back is termed *negative* because it tends to cancel an original error in performance.

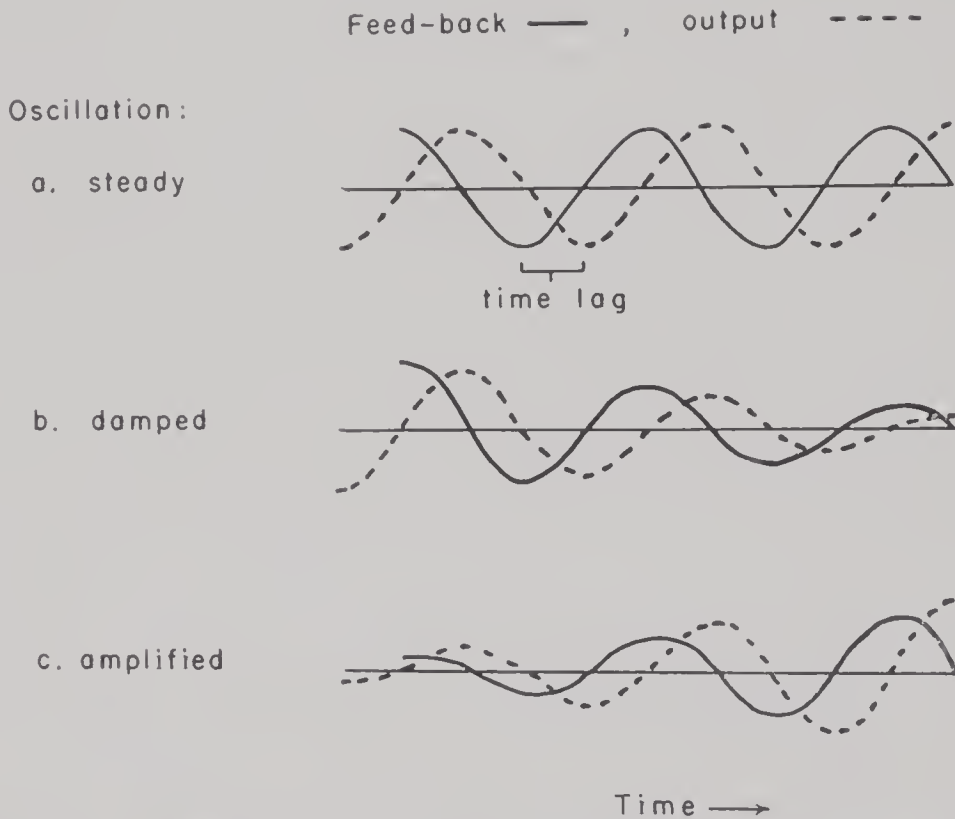


FIG. 1-13. TYPES OF OSCILLATION IN A SELF-REGULATING MECHANISM

The oscillating error of performance in a system or mechanism is shown by the broken line; the negative feed-back by the continuous line. The time lag between the two is the distance by which the two nodal points are separated. Each succeeding cycle of performance or output is regulated by the preceding feed-back signal.

In *a* the oscillation is steady, each deviation of performance being cancelled by an opposite and equal error. This system is perfectly adjusted to maintain a steady state. In *b* the oscillation is being damped, i.e., the error is being progressively diminished and the steadiness of the system is increasing. In *c* the opposite is true: the error is increasing, the system is becoming unsteady and losing its self-regulatory control. (Modified from Tustin (20d).)



performance (a), the oscillation of the system about a mean is steady, i.e., a steady state is maintained. When the feed-back signal leads to diminishing error of performance (b), the oscillations are damped and the steadiness of the system is increased. When the opposite is true and the oscillations are amplified (c), the system is becoming less steady. Such a process unchecked in a biological system is the antithesis of homeostasis and leads to death.

In the example of water balance as a self-regulating physiological mechanism the servomechanisms are complex. The output of water in excess of electrolyte controlled by the antidiuretic hormone in the kidney, produces a rise in extracellular electrolyte concentration. The rise in this concentration feeds back to the osmoreceptors in the hypothalamus to stimulate the production of antidiuretic hormone (ADH) in the supraoptico-hypophyseal system, and so the error in output of water tends to be corrected. At the same time this system is linked to regulation of intake through thirst. Hypertonicity of extracellular fluid with resultant cellular dehydration stimulates thirst and increased intake of water as well as the production of ADH, (14f, 21a, b). Thus both intake and output are regulated to minimize error in water content of the body. However, water turnover is conditioned by solute, especially sodium, intake and output. Here the whole chain of regulatory processes cannot be so readily described because, as indicated in the preceding section, much remains to be learned. But solute intake is certainly related to appetite and it is not surprising that the centers for control of appetite apparently are located in the hypothalamus (21c, d) in close proximity to those for thirst and antidiuretic hormone production. It is tempting to consider the possibility of describing all these linked servo-

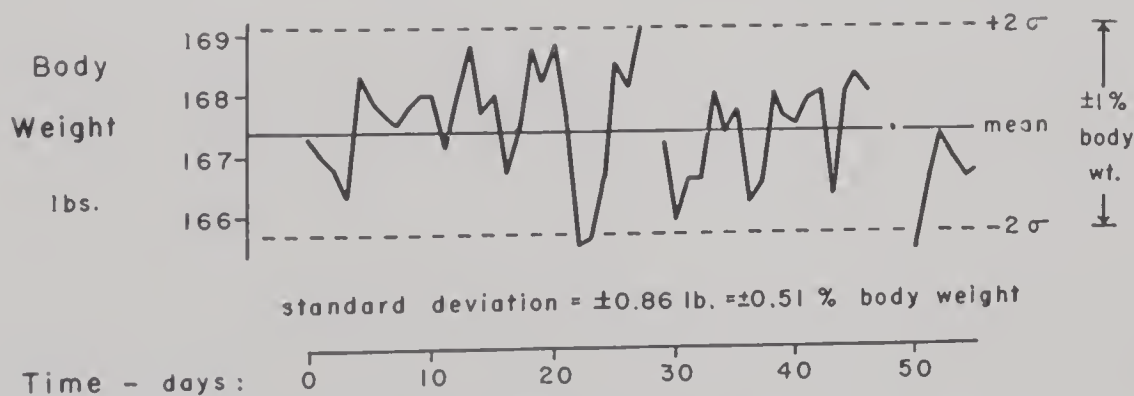


FIG. 1-14. OSCILLATION OF A STEADY STATE: THE DAILY BASAL BODY WEIGHT OF A NORMAL SUBJECT

The daily basal body weight of a healthy adult, one of the authors, is shown as determined 53 times over 56 consecutive days. The standard deviation was  $\pm 0.86$  lbs or  $\pm 0.51$  per cent of the body weight. This represents maintenance of a steady state within  $\pm 1$  per cent of the total body weight. (Unpublished studies.)



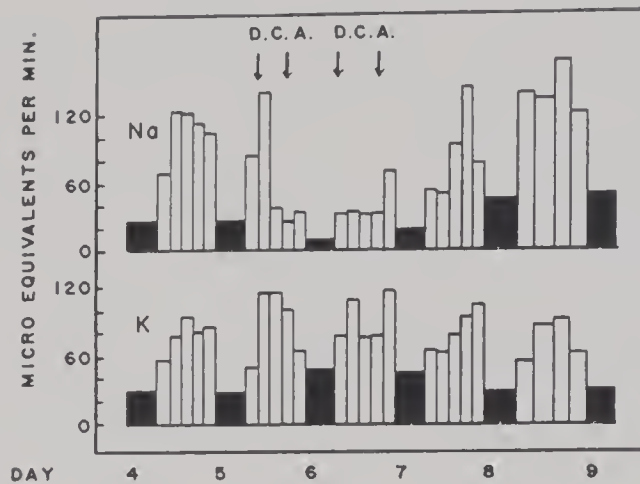


FIG. 1-15. DIURNAL VARIATIONS

During each night (solid columns) a marked drop in the urinary output of sodium and potassium was recorded in this subject. DCA decreased sodium output and increased potassium output but did not obliterate the rhythm. (From Stanbury and Thomson (22b).)

mechanisms in the organism in terms of control of energy exchange with the environment.

Thus the total body content of solids and fluids is maintained in the healthy adult at a constant level with oscillation about a mean. In figure 1-14 the daily basal weight of one of the authors is charted over a period of 56 days. The relative constancy again indicates minor but definite fluctuations about the mean value. In figure 1-15 is shown the typical diurnal variations of certain body fluid constituents. The causal sequence of the variation is not clear (22a, b) but they undoubtedly represent an oscillation within a steady state. The same may be said for variations in the serum concentration of many solutes as observed over varying periods of time (see chapter 4).

In conclusion, we are brought again to the opening section of this chapter. The dynamics of the body fluids are one aspect of the integrated function of the organism by which a steady state is maintained with the aid of exogenous energy ultimately derived from the sun. Matter, whether once or continually created in the universe, ever moves in the one direction of greater randomness or increased entropy. Thus, in thermodynamic perspective, man becomes with all other living organisms an island of "negative entropy" breasting an inexorable downhill flow of energy in the universe.

**SUMMARY:** The fluid of the body is distributed into two main phases. Of the two, the cellular phase is the larger while the extracellular phase includes interstitial fluid, the connective tissue spaces, and the plasma. Fluids

are transferred within the body by diffusion along concentration gradients, by osmosis in response to alterations in the number of particles in solution restrained by membranes, by expenditure of energy for the active transport against concentration gradients, and by mass movement of fluid as a result of hydrostatic pressure. These types of movements are to be differentiated from flux which is the rate of movement of an ion in one direction during diffusion, osmosis, or active transfer.

External exchanges between the organism and the environment are effected through the gastrointestinal tract, kidney, lungs, skin and at times other body surfaces. The volume, composition, and distribution of body fluids is maintained constant within narrow limits by regulators or feedback systems which act largely upon or through the kidney.

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“And God said, Let the waters bring forth abundantly the moving creature that hath life. . . .”  
*Genesis*

## *Chapter 2*

# **PALEOCHEMISTRY, EVOLUTION, AND COMPARATIVE PHYSIOLOGY OF THE BODY FLUIDS**

### **I. Introduction**

Adequate comprehension of the composition and dynamics of man's body fluids requires consideration of their place in Nature, past and present. That man is a creature of his planetary environment is nowhere more evident than with respect to the fluids of his body, for some of the very elements of one are the basic constituents of the other. Indeed, the fundamental properties of these elements, water, carbon dioxide, certain inorganic ions, and protein, have conditioned alike the evolution of life and the evolution of the earth, and they in turn have conditioned one another. These interactions of the processes of geochemistry and physiology are reflected in the structure and function of the body fluids of living organisms which bear to this day the imprint of their ancient cradle in the primordial seas.

Ever since the early recognition that sodium and chloride are the predominant ions both in the extracellular fluid of vertebrates and in the water of the oceans (fig. 2-1), it has been suspected that the former must have evolved from a marine environment. This suggestion, made by Bunge in 1889 and Quinton in 1897, was extended by Macallum in 1903 and 1926 to his well-known hypothesis that the inorganic pattern of the body fluids of invertebrates and vertebrates is a reproduction of the relative ionic composition and total ionic concentration of the sea water of the particular geological period in which their prototypes first appeared (1a-d). Since then many studies (including those of Conway, Pantin, Dakin, Smith, and Krogh) of the ancient, or “paleo-”chemistry of the earth's crust and its seas (2a-d), and of the relationships in the past and present between living organisms and their environments (3a-c), have led to a modification of this hypothe-



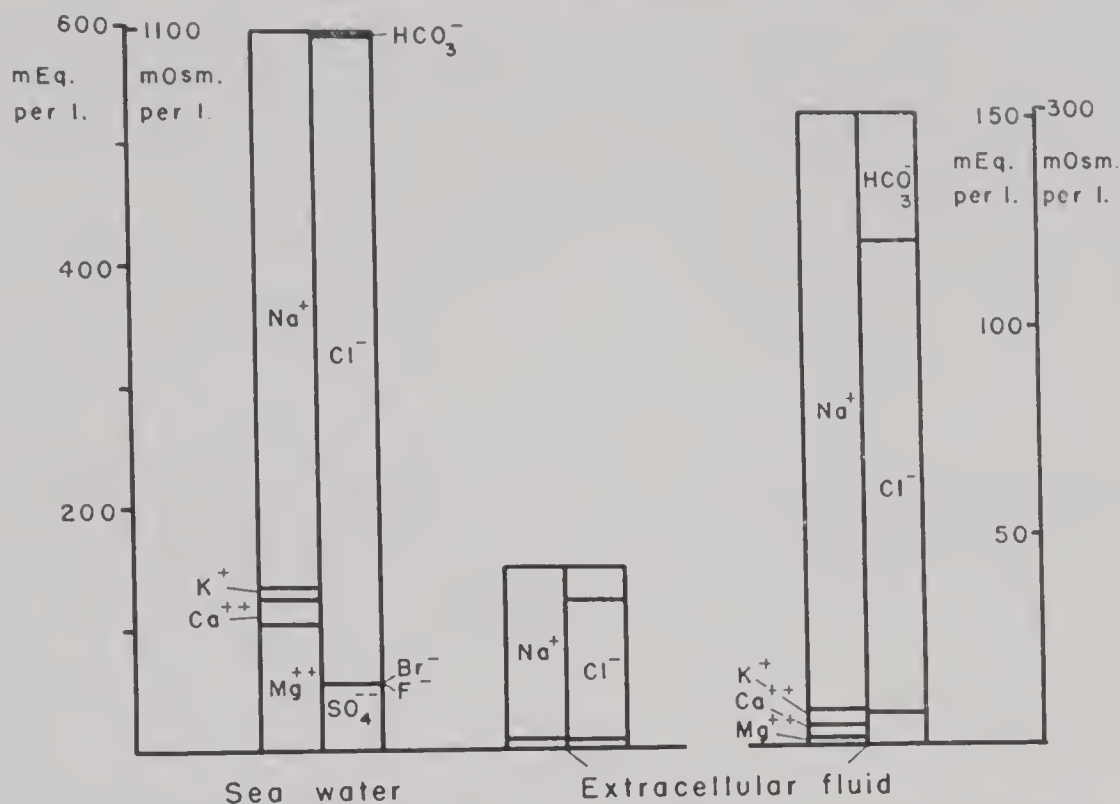


FIG. 2-1. TOTAL IONIC CONCENTRATION AND RELATIVE IONIC COMPOSITION OF SEA WATER AND OF HUMAN EXTRACELLULAR FLUID

On the left are plotted on the same scale the concentrations of cations and anions in sea water and in the interstitial portion of the extracellular fluid of man. On the right this portion of the extracellular fluid is re-plotted on a larger scale to show the similarity of its relative ionic composition to that of sea water. Values for the composition of sea water are taken from Svedrup, Johnson and Fleming (16).

sis. The evolution of homoiosmotieity, or the dynamic maintenance of an osmotically independent internal milieu (told with clarity in the writings of Homer Smith, Baldwin, Florkin, and Prosser and associates (3c, d, 4a-c)), has involved many modifications of the concentration and composition of that milieu, as the organs of exchange have become adapted to the requirements for internal stability in the face of environmental vicissitudes. Nevertheless, as Pantin states (3a), the composition of ancient sea water was a particularly fit environment for the origin and development of protoplasmic systems and in this sense the composition of present day extracellular fluids can be considered to reflect a marine ancestry.

## II. Paleochemistry

### A. Fitness of the Environment and the Origin of Life

Precursors of protoplasm originated somehow and sometime in a dim pre-Cambrian era more than 1000 million years ago (5a-c). It is a matter of speculation as to how the organic materials present first acquired the free energy necessary for reproduction and growth, but most students of the

subject agree that life must have begun in the sea, the "hot soup" of Haldane and the colloidal ooze of Oparin.

In addition to providing the necessary conditions for the origin of life, the ocean possessed unique properties for a continuing environment: mobility, richness in dissolved substances, and stability of physico-chemical conditions. To L. J. Henderson we owe the concept of the *fitness of the environment* as bearing a necessary and reciprocal relationship to the fitness of the organism (6d). Henderson pointed out that water, carbonic acid, and their constituent elements manifest great fitness for their biological role. The thermal properties of water, its solvent power, dielectric constant, and surface tension, provide maximal fitness for processes of life in terms of ubiquity, constancy of temperature, and variety of chemical, electrical, and colloidal phenomena. The solubility of carbon dioxide in water, its buffering capacity as a weak acid, and its volatility likewise make for maximum fitness in terms of mobility, ubiquity, and constancy of hydrogen ion concentration. The chemical compounds containing hydrogen, carbon, and oxygen possess unique properties for serving as sources of matter and energy for the processes of metabolism.

In such a fit environment in the ancient seas protein somehow was synthesized and energy was captured from the sun by photosynthesis and stored in the organic esters of phosphoric acid. To maintain electroneutrality the negatively charged protein required positively charged cations. Thus cationic components of the marine fluid environment became important conditioning factors to the internal fluids of the living organism.

### *B. The Chemical Evolution of the Ocean*

Since sodium predominates over potassium in the sea, and potassium over sodium in sedimentary rocks (table 2-I), it is apparent that these cations are distributed differentially on a geochemical as well as on a biological level. In the less technical language of Fenn (6b), "potassium is of the soil and not of the sea; it is of the cell but not of the sap." Any inquiry as to possible relationships between these two phenomena leads to a consideration of the chemical evolution of the ocean.

The papers of Conway (2a, b, d) and their criticism by Hutchinson (2c) appear to present the most exhaustive recent analysis of geochemical data in relation to oceanic evolution and biologic exchanges of ions. The basis of this analysis is the determination of the chemical composition of igneous and sedimentary rocks, and of river water eroding such rocks (table 2-I), and the calculation of the thickness of the sedimentary strata by measurements of radioactivity. From these geochemical data estimates were made of the total amounts of inorganic substances removed from the earth's crust at any given time since the initial condensation of water in the

TABLE 2-I.

RELATIVE IONIC COMPOSITION OF IGNEOUS ROCK, TOTAL SURFACE ROCK, RIVER WATER DRAINING THESE TWO TYPES OF ROCK, AND OCEAN WATER* (From Conway) (2a,b)					
ION	ROCK		RIVER WATER <sup>§</sup>		OCEAN Water
	Igneous	Total Surface <sup>#</sup>	Igneous	Total Surface <sup>#</sup>	
Na	100	100	100	100	100
Mg	142	334	61	225	23
Ca	146	454	238	897	5
K	54	133	34	45	2
Cl	1	1	6	1	117
SO <sub>4</sub>	3	23	8	212	12
C (as CO <sub>3</sub> , or HCO <sub>3</sub> )		113	414	1040	1

\* Data are given as equivalents associated with 100 equivalents of sodium  
§ River water is corrected for contamination with marine salts in rain.  
# Total surface rock is approximately 75 per cent sedimentary

earth's atmosphere. The results of this calculation, with respect to the major oceanic ions, are shown in figure 2-2. The concentrations of ions in the ocean waters are plotted not against time, but against the thickness of sedimentary rock, unity representing the present maximum thickness of approximately 1,050,000 feet that has accumulated over some 1750 million years.<sup>1</sup> On the assumption of a constant volume of water and of a volcanic source of the chloride, chloride and sodium have steadily accumulated until some 141 geograms ( $141 \times 10^{20}$  grams) of sodium ion have been deposited in the sea, producing a concentration of 470 to 480 mM. per liter. Calcium, which is the most abundant single cation in igneous rock, on reaching the ocean has been largely precipitated and sedimented as cal-

<sup>1</sup> From the rate of addition of solutes in river water, Joly calculated the age of the ocean to be approximately 80 to 90 million years (7a). Conway points out that this is much lower than the now accepted value of roughly 1500 to 2000 million years, derived from measurements of radioactivity. He suggests that correction should be made for contamination of river water with marine salts in rain, for flooding, and for the probability that the present day erosion rate must be higher than the mean rate over geologic time. This latter correction is due to the above-average elevation of land masses in the present geologic period coupled with the artificial denudation of the land of its forests by man. If the rate of solute accretion from the Amazon River is used (river water that drains mainly flat untouched jungle), a value of 2,350 million years is reached for the age of the ocean.



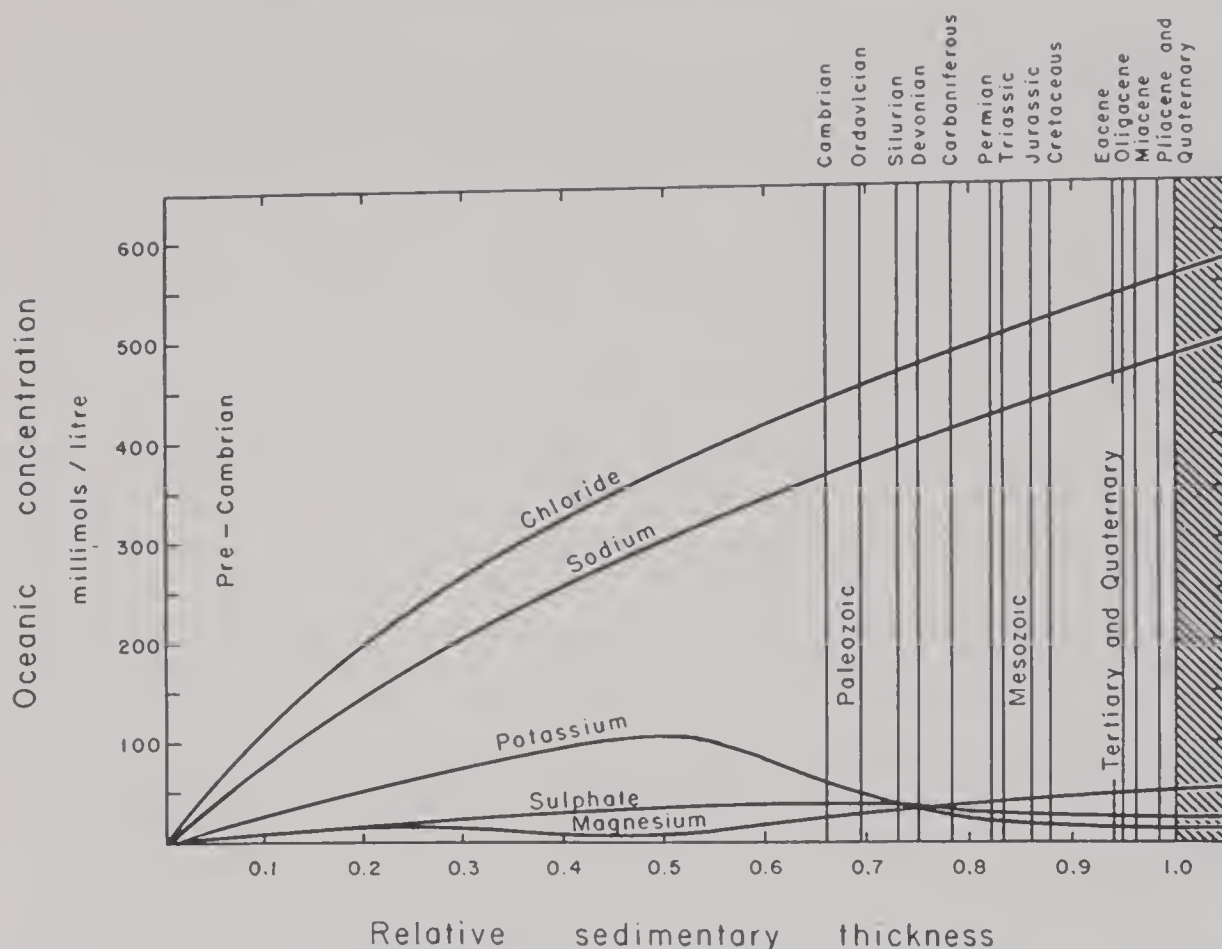


FIG. 2-2. THE CHEMICAL EVOLUTION OF THE OCEAN

On the assumption of a constant volume and of a volcanic source of chloride, Conway has calculated, from analyses of various types of rock and of river water, the concentrations of the principal ions in the ocean over geologic time. These concentrations are plotted, not against time *per se*, but against the relative thickness of sedimentary rocks which have been laid down since the beginning of erosion of the earth's crust; (unity represents the total thickness at the present time and the cross-hatched area extrapolation into the next 100 million years).

The steady accumulations of chloride and sodium are contrasted with the relative and absolute removal of potassium. (From Conway (2b).)

cium carbonate and sulfate.<sup>2</sup> Magnesium likewise has been removed as the carbonate but to a lesser extent, so that today it is the second largest cationic component of the ocean. Had the chloride been present in the atmosphere and in the condensed sea water in constant amounts (a slightly less likely hypothesis than that of volcanic origin), somewhat larger quantities of magnesium and calcium would have been in solution during the earlier periods of oceanic evolution.

<sup>2</sup> Conway believed that the carbon dioxide necessary for the formation of calcium and magnesium carbonate must have been of volcanic origin. If it originally had all been in the atmosphere, the CO<sub>2</sub> pressure as late as the Jurassic period would have been eight times the present value and presumably incompatible with the life of such vertebrates as the dinosaurs.

The relative and absolute removal of potassium from the oceans and its sequestration in sedimentary rock is in striking contrast to the fate of the sodium derived from the same igneous rock source. Potassium is carried to the sea in river water in amounts that are 35 to 45 per cent of the accompanying sodium (table 2-1) yet only 2 per cent is in solution in the sea today. Therefore approximately 100 geograms ( $100 \times 10^{20}$  grams) of potassium must have been removed over the course of geologic time. The clay mineral, illite, which constitutes about 20 per cent, or 1600 geograms, of the total 7400 geograms of sedimentary rock, contains potassium in amounts of this order of magnitude. Potassium is also found in glauconite, a similar mineral formed from the shells of dead foraminifera. It would appear, therefore, that potassium has been steadily sequestered in sedimented illites since the beginning of oceanic evolution. This removal of the ion was accelerated with the advent of organic life sometime in the late pre-Cambrian era, and since the Mesozoic era onward this biologic deposition in glauconite may have been the principal mode of potassium removal from the ocean. It is also possible that the presence of organic material facilitated the incorporation of potassium into the illite. Thus we have an example of the geochemical evolution of the ocean being modified by the life that it supports.

The subtraction of potassium from the ocean has been equivalent to the addition of hydrogen ion. The effect of this acidification of a relatively alkaline ancient ocean must have been to increase the total amount of calcium and magnesium in solution while at the same time sulfates and carbonates were precipitated out as calcium and magnesium salts. This would permit or enhance the calcification of fossils from Cambrian time onward, and is another example of geochemical and biological interplay.

Conway has suggested that the smaller diameter of the hydrated potassium ion accounts for its differential sequestration over sodium in both the mineral clays and the cells of living organisms. In illite this diameter is critical for entry and binding between the silica sheets of the lattice in positions where the quadrivalent  $\text{Si}^{++++}$  has been replaced by the trivalent  $\text{Al}^{+++}$ . In the living cell the smaller hydrated diameter may also promote the more rapid entry of potassium as compared with sodium and the retention of potassium while the sodium is actively extruded. The latter process, however, requires energy in the system (see chapter 1) and to that extent is not analagous to the sequestration occurring in the sedimentary illites. But the degree and ubiquity of the disparate distribution of these two cations on the geochemical and biological levels naturally suggest the possibility that some fundamental physico-chemical factors are common to both processes.<sup>3</sup>

<sup>3</sup> It is interesting to note that the other alkali metals, lithium, rubidium, and

TABLE 2-II.

IONIC CONCENTRATIONS IN THE OCEAN AT VARIOUS GEOLOGICAL PERIODS*, AND IN VERTEBRATE EXTRACELLULAR FLUID (From Conway (2b))				
ION	MID PRE-CAMBRIAN SEA#	EARLY ORDOVICIAN SEA§	OCEAN TODAY	VERTEBRATE EXTRACELLULAR FLUID (HUMAN PLASMA)
	mM./l.	mM./l.	mM./l.	mM./l.
Na	298	379	478	144
K	104	51	10	5
Ca	2	7	11	5
Mg	11	38	55	2
Cl	298	441	559	103
SO <sub>4</sub>	54	40	29	1
HCO <sub>3</sub>	(13)	(5)	(2)	28
PO <sub>4</sub>			Tr.	2

\* Based on the hypothesis of a volcanic origin of chloride

# Approximate time of development of unicellular organisms

§ Period of emergence of vertebrates

() HCO<sub>3</sub> concentration with the present-day atmospheric pressure of CO<sub>2</sub>

### C. Sea Water and the Internal Environment

The probable course of chemical evolution of the ocean as set forth by Conway does not support the hypothesis of Macallum (1d) that present-day extracellular fluids reflect the ionic concentrations of the ancient seas in which a given species first developed. At the time of differentiation of vertebrates in the Cambrian or Ordovician periods the salt content of the ocean was at least 60 to 70 per cent of the present concentration in sea water; yet most vertebrate extracellular fluids are less than one-third of that concentration (fig. 2-2, table 2-II). Furthermore, the magnesium content of vertebrate extracellular fluid is proportionately and absolutely much smaller than that in the Paleozoic seas. To these objections are joined the more cogent data from studies in comparative physiology by Dakin, Smith, and many others who have clearly demonstrated that osmoregulation is

cesium, present in relatively minute amounts, are also removed quantitatively from the sea into the clay minerals (2c). On experimental administration to animals and man, lithium, which lies below sodium in the periodic table, has a volume of distribution which lies between those of sodium and potassium (7b, c); on the other hand, rubidium, which is above potassium in the periodic table and has a smaller hydrated diameter, substitutes for potassium in, or displaces potassium from, intracellular fluid (7d, e). The effect of rubidium on the electrocardiogram is similar, but not identical, to that of potassium (7f).



a dynamic process with many species able to make rapid adjustments to changes in their osmotic environment. It is not the composition of the body fluids that evolves, therefore, but rather the organs of active exchange which regulate that composition.

### III. Evolution of the Kidney and the Body Fluids

#### *A. Regulatory Mechanisms and the Environment*

The history of the earth has been one of ever-changing surface contour and climate (8a, b). Periodic upheavals of major mountain systems, marking the geologic revolutions, have alternated with the erosion and flattening out of the land masses; time and again the seas have flooded over the dry land only to recede; hot, moist climates with lush vegetation have alternated with aridity, coldness, and sometimes glaciation. In such a world the survival of living organisms has depended directly upon their adaptation to these changing conditions of the external environment.

Such adaptation has been paramount in respect to osmoregulation, which constitutes a major chapter in the history of biological evolution from unicellular organisms to highly differentiated vertebrates. The mechanisms of osmoregulation have been classified by Prosser *et al.* (4c) as those that provide:

1. Limited permeability to water,
2. Limited permeability to solutes,
3. Secretion (in or out) of salt against a gradient,
4. Secretion (in or out) of water against a gradient,
5. Storage of water or solute.

Some of these adaptive mechanisms maintain a dynamic steady state and so require the expenditure of energy (see chapter 1). Even in the simpler poikilosmotic invertebrates whose internal osmolar concentration adjusts to that of the external medium, some restriction is placed on water and solute exchanges (and therefore on changes in volume). The more complex homoiosmotic organisms utilize various combinations of these mechanisms to maintain an internal osmolar concentration and ionic pattern that is independent of the external medium.

Since with increasing zoological complexity the kidney has become the principal site of these regulatory exchanges, attention has been centered on the paleontological and paleoecological role of this organ. Many students and investigators have contributed to the elucidation of this role but none more so than Homer Smith, whose classical accounts provide the most detailed analyses and lucid expositions available on the subject (3c, d, 8c).

#### *B. Adaptation to Fresh Water (Early Paleozoic)*

Out of the multiplicity of invertebrate life in the early seas emerged the ancestor of the vertebrates, the protovertebrate. This emergence probably

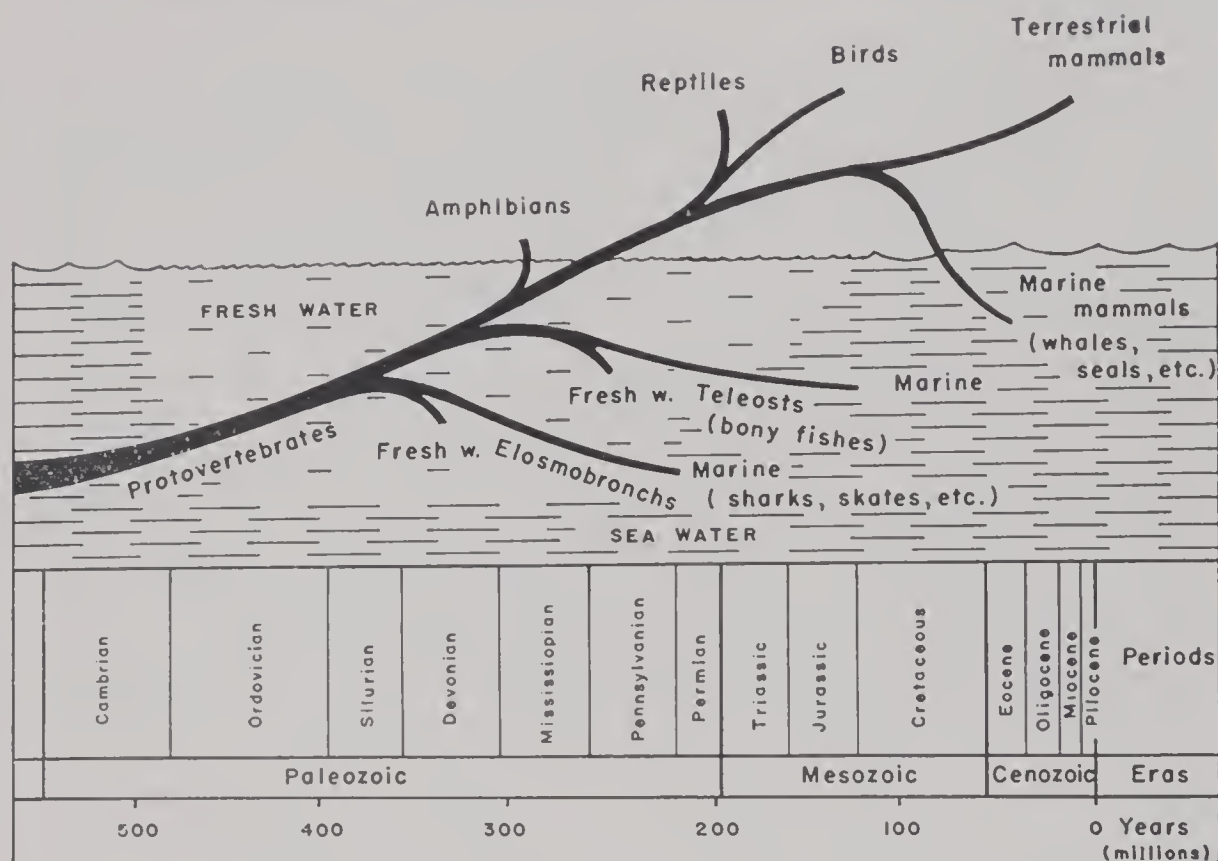


FIG. 2-3. THE EVOLUTION OF VERTEBRATE SPECIES AND THEIR HABITATS

The course of development of the vertebrates is plotted in relation to the geologic timetable shown at the bottom of the chart. Fresh water, marine, and terrestrial environments are indicated.

The major development took place in the Paleozoic era in fresh water with subsequent adaptation to marine and terrestrial habitats. (Modified from Smith (3c, d).)

took place in the Cambrian period which was ushered in by the Grand Canyon disturbance. It has been postulated that this hypothetical ancestor had a flexible backbone which was useful in swimming against the more rapidly moving water draining the uplifted land. In any case, a few fossils of his heavily-armored descendants, the ostracoderms, or ancient fishes, have been found in Ordovician sediments and the evidence indicates that these early vertebrates were inhabitants of fresh water (fig. 2-3).

The morphologic and physiologic adaptation of these early vertebrates to their fresh water habitat can be surmised. Presumably the osmolar concentration in their body fluids approached or equalled that of the Paleozoic seas. The heavy armor of the fossils indicates the development of an impermeable exterior which would have reduced the osmotic inflow of water. Gills and mouth, however, were permeable, and in relation to the need to excrete water the segmented kidney was developed. Filtration of water from the blood stream was facilitated by juxtaposition of a capillary tuft to the coelomostome or mouth of the excretory tubule draining the coelom or body cavity. Thus was developed the primitive glomerulo-tubular kidney with a renal-portal blood supply, and in turn, the ability to live in fresh water.

### C. Re-adaptation to Marine Environment

**1. Elasmobranchs (late Paleozoic).** After the Caledonian upheaval at the beginning of the Devonian period, alternating drought and flooding forced some of the fresh-water fishes either to become mud-dwelling lung-fish or to return to the salty seas (fig. 2-3). The latter were the elasmobranchs or the ancient shark family of cartilaginous fishes (Chondrichthyes) that has survived to this day.

The functional adaptation of these species to the new salty medium was unique. Endowed with a primitive kidney that was "designed" to excrete water in a hypotonic medium, a different osmotic defense was developed against the dehydrating effect of the hypertonic seas, namely, a physiologic uremia. The active reabsorption of urea by the renal tubule, plus the impermeability to urea of the respiratory membranes and gills, led to a concentration of urea in the body fluids of more than 2 per cent, and a total osmolar concentration that was slightly higher than that of the surrounding sea water (fig. 2-4). This resulted in the absorption through the gills, and

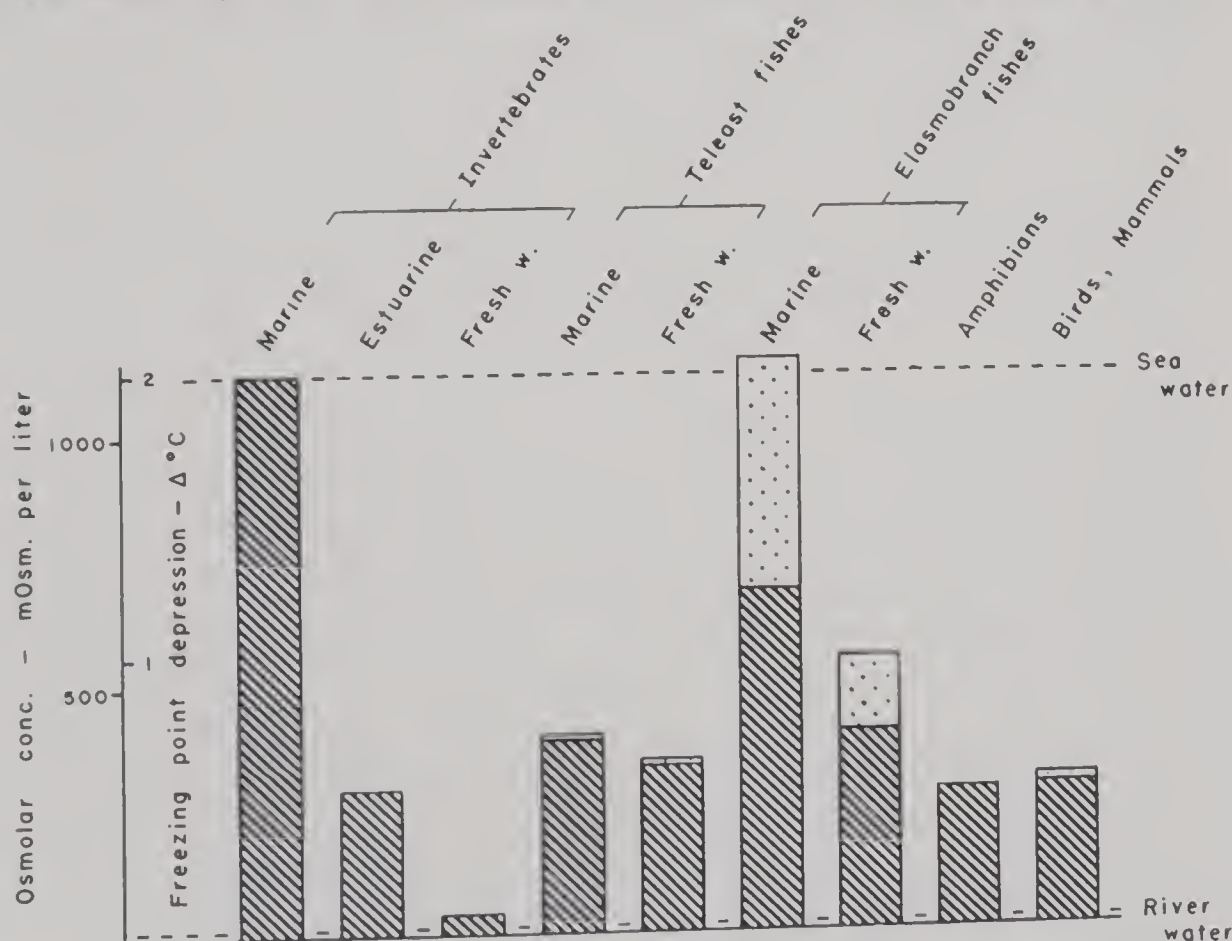


FIG. 2-4. COMPARISON OF THE TOTAL OSMOLAR CONCENTRATION OF BODY FLUIDS OF VARIOUS INVERTEBRATES AND VERTEBRATES WITH THAT OF SEA WATER AND OF RIVER WATER

Cross-hatched areas represent inorganic ions and dotted areas urea. (Modified from Baldwin (4a).)



in the excretion through the kidney, of small amounts of water. Some members of this group have become readapted to brackish or fresh water (the sawfish, *Pristis*, in Malaya). In these the urea concentration is much lower (fig. 2-4), the water absorption is greater, and larger volumes of urine are excreted. The latter is effected by an increase in glomerular filtration which occurs as the fish passes from salty to fresh waters.

**2. Teleost fishes (late Paleozoic or Mesozoic).** Toward the end of the Paleozoic era the teleost or bony fishes (Osteichthyes) evolved in the fresh water of that time, and many still live in their fresh water habitat. However, between the end of the Paleozoic and the beginning of the Cenozoic, many of the teleosts moved to the oceans and developed a new mechanism of osmoregulation in defense of their internal environment (figs. 2-3, 2-5). This was an adaptation of the gill, with cells which actively separate and excrete the sodium and chloride ingested from the sea. The diminished amounts of water left behind for excretion by the kidney placed less of a premium on glomerular filtration and the kidneys of many of these species became aglomerular. It was the study of these aglomerular teleosts that led E. K. Marshall and his associates (8d) to the establishment of tubular secretion as a physiologic entity, for these tubular kidneys excreted many of those substances which in other species are found in the urine passed from glomerulo-tubular nephrons. In the marine teleosts the principal inorganic ions in the urine are magnesium and sulfate, sodium and chloride being excreted by the gills. The urine is hypotonic and scanty in volume since the amount of sea water ingested is kept to a minimum.

Some members of this group, such as eels and salmon, move back and forth between fresh water and salt water; while much remains to be learned of the physiologic adjustments that permit such lability of habitat, it is probable that these adjustments include wide variability in glomerular filtration as the need varies for the excretion of water.

#### *D. Adaptation to Air and Dry Land*

**1. Amphibians (late Devonian).** This adaptation was first achieved by the Amphibia and ante-dated by a few geologic periods the teleosts' invasion of the sea. In the arid climate of the late Devonian the heavily armored ostracoderms and fresh-water fish propelled themselves on their ventral fins from puddle to puddle and so beyond the edge of their fresh water habitat. From some of their modern descendants, the frogs and salamanders, we learn of the character of their fluid balance mechanisms. These were, and are, of two kinds: 1) the skin became passively permeable to water and developed the ability to actively absorb salt, and 2) glomerular filtration (and hence renal water excretion) could be intermittently reduced by constriction of the glomerular arteriole. Both of these mechanisms come

under the control of the pituitary gland, an early instance of hormonal control of water balance. The amphibians flourished in the warm swamps of the late Carboniferous (Pennsylvanian) period; but most of them (excepting toads and salamanders) never developed the ability to lay eggs away from, or to leave for long, the aqueous environment from which they arose.

**2. Reptiles and birds (Mesozoic).** As the amphibians left the water in the arid climate of the Devonian period, so the ancestors of the reptiles emerged from their aqueous habitat in the aridity of the Permian. Unlike amphibians generally, however, the reptiles developed the ability to reproduce on land and so achieved a real independence in their terrestrial existence. This adaptation consisted of the amniotic egg, an adaptation which was essential to the terrestrial evolution of birds and mammals as well. The amniotic egg, within a covering impermeable to water, provided a closed aquatic environment for the embryo as well as a chorion and yolk for respiration and nourishment and an allantoic sac for metabolic end-products. In addition, the reptiles and birds achieved another mechanism for the conservation of water by becoming uricotelic or uric-acid-excreting, i.e., uric acid replaced urea as the end-product of nitrogenous catabolism. Uric acid may be excreted in the semi-solid state, and in the cloaca of the bird a high degree of water conservation is attained by the reabsorption of water and the excretion of a hypertonic semi-solid urine.

The evolution of a kidney able to elaborate urine that is hypertonic in relation to the plasma and extracellular fluid first took place in the birds. This was more imperative in birds than in reptiles because the birds also developed into homoiothermic creatures. While this physiologic characteristic increased their independence of the environment, it also increased their need to conserve water. The dissipation of body heat involves the vaporization of body water, a process that plays an important part in the water balance of the other class of warm-blooded vertebrates elaborating a hypertonic urine, the mammals.

**3. Terrestrial mammals.** In the Permian period of aridity and cold, the mammals, like the birds, became differentiated from the reptiles by development of the ability to regulate body temperature and to conserve water. During the Jurassic and Triassic, the "Age of Reptiles," their multiplication was slow; at the end of the Cretaceous and during the early part of the modern era (the Cenozoic), the mammals rapidly attained a dominant position. Their metabolic demands for food required them to keep awake and active, and their metabolic heat production required conservation of water for heat expenditure. The superior mammalian organs, evolved in the presence of these requirements, were the brain and the kidney.



The mammalian kidney excels in the conservation of water. Unlike the uricotelic birds, the mammals retained urea as the end-product of nitrogen metabolism, and the high solubility of urea resulted in larger amounts of water being excreted. The higher blood pressure and the faster rate of circulation associated with the homoiothermic state led to a greater rate of glomerular filtration. As a consequence, the mammals evolved a kidney unequalled in its capacity to filter and to reabsorb water. This maximal ability to reabsorb water was associated morphologically with the development of the "thin segment" or loop of Henle in the renal tubule separating the proximal and distal segments, and physiologically with the supra-optico-hypophyseal system for the elaboration of anti-diuretic hormone. These mechanisms permit the mammal to excrete a minimum of water in a urine that is hypertonic in respect to the body fluids, and constitute an excellent adaptation to life on the dry land and in the air (table 2-III).

#### *E. Present-day Adaptations*

The evolution of osmoregulatory mechanisms in vertebrates has just been reviewed and hence these mechanisms as they exist in present-day species need not be elaborated further. The total osmolar concentrations of the body fluids of invertebrates and vertebrates are compared with those of sea water and river water in figure 2-4. For both invertebrate and vertebrate species, the adaptive mechanisms for maintenance of fluid balance in various osmotic environments are tabulated in table 2-III and schematically presented in figure 2-5. Only certain modern adaptations are commented upon further in the following paragraphs; for the most complete and detailed presentation of the whole subject the reader is referred to the book of Prosser and associates (4e).

**1. Invertebrates** vary widely in their adaptation for osmoregulation. Some species adjust osmotically fairly completely to their external environment, but others exert a limitation on such adjustment in terms of water shifts and changes in volume. The body fluids of marine invertebrates tend to be isosmotic with sea water while estuarine and fresh-water forms maintain much lower internal concentrations (fig. 2-4). The latter two, however, are always higher than their brackish or fresh-water environments and thus point to a certain degree of internal regulation. Even in the marine invertebrates Robertson (9a) has demonstrated a wide variation in the regulation of individual ions. In the more primitive and less active phyla, such as the coelenterates, echinoderms, lamellibranchs, and others, there is a slight accumulation of potassium and calcium and a diminution of sulphate relative to sea water (sodium, chloride, and magnesium are in equilibrium). The more active decapod Crustaceans and cephalopod Molluscs show a greater degree of regulation with accumulation of sodium and a marked reduction



TABLE 2-III.

ADAPTIVE MECHANISMS FOR MAINTENANCE OF FLUID BALANCE IN VARIOUS OSMOTIC ENVIRONMENTS			
OSMOTIC ENVIRONMENT PROBLEM OF FLUID BALANCE	SPECIES	FLUID BALANCE MECHANISMS	SEE FIGURE 2-5
Sea water - hypertonic medium prevention of dehydration	Marine invertebrates (e.g., molluscs, Maia)	Poikilosmotic: in some, volume regulated by intake and output of salt	a
	Marine elasmobranchs (e.g., sharks, rays)	Urea hypertonicity Gills impermeable to urea and renal tubular cells actively reabsorb urea. Water through gills, scanty hypotonic urine (glomerular degeneration)	
	Marine teleosts (bony fishes, e.g., cod, herring)	Ingestion of water and salt, by active excretion of salt by gills, scanty hypotonic urine (glomerular degeneration)	b
	Marine mammals (e.g., whales, seals)	Feed on plankton or isotonic teleosts, no ingestion of sea water, active renal reabsorption of water, hypertonic urine	c
Fresh water - hypotonic medium prevention of overhydration	Fresh-water invertebrates (e.g., crab, Carcinus)	Relatively poikilosmotic: low permeability to water, selective absorption of salts and excretion of water	d
	Fresh-water elasmobranchs (e.g., sawfish, Pristis)	Urea hypertonicity of lesser degree, copious hypotonic urine	
	Fresh-water teleosts (e.g., trout)	Water and salts absorbed through skin, copious hypotonic urine	e

Fresh water and air prevention of alternating overhydration; desiccation	Amphibia (e.g., frog)	Active sodium and passive water absorption through skin, copious hypotonic urine	f
Dry land and air, prevention of desiccation	Reptiles	Ingest water; excretion of uric acid (uricotelic) instead of urea permits scanty urine	
	Birds	Ingest water, uricotelic - extreme water conservation in kidney and cloaca → semi-solid hypertonic urine	g
	Terrestrial mammals	Water by ingestion and oxidation, active water conservation in kidney → hypertonic urine	h
	Terrestrial arthropods (e.g., insects, spiders)	Impermeable cuticle; ingested water lost by evaporation through spiracles (minimized by humidity), semi-solid hypertonic urine	

of magnesium, in addition to the gradients mentioned above. It is clear, therefore, that in many invertebrates the poikilosmoticity is only relative and that steady states are maintained with respect to both total osmolarity and individual ionic levels.

**2. Marine mammals and birds** have returned to a habitat devoid of fresh water and thus present an interesting problem in the regulation of water balance (3d, e, 4c, 9b, e). The mammals include the seals, walruses, and sea-lions, and the whales, porpoises, and dolphins. In these animals the total osmolar concentration of the body fluids is slightly higher than in the terrestrial mammals, but is still far below that of sea water. The urine may reach, or exceed, the latter concentration, but there is no evidence that the kidney possesses concentrating powers that are much different from those in the kidneys of other mammals to which fresh water is available. Since the low magnesium and sulfate content of intestinal residues indicates that sea water is not ingested, the answer must lie in the relation-

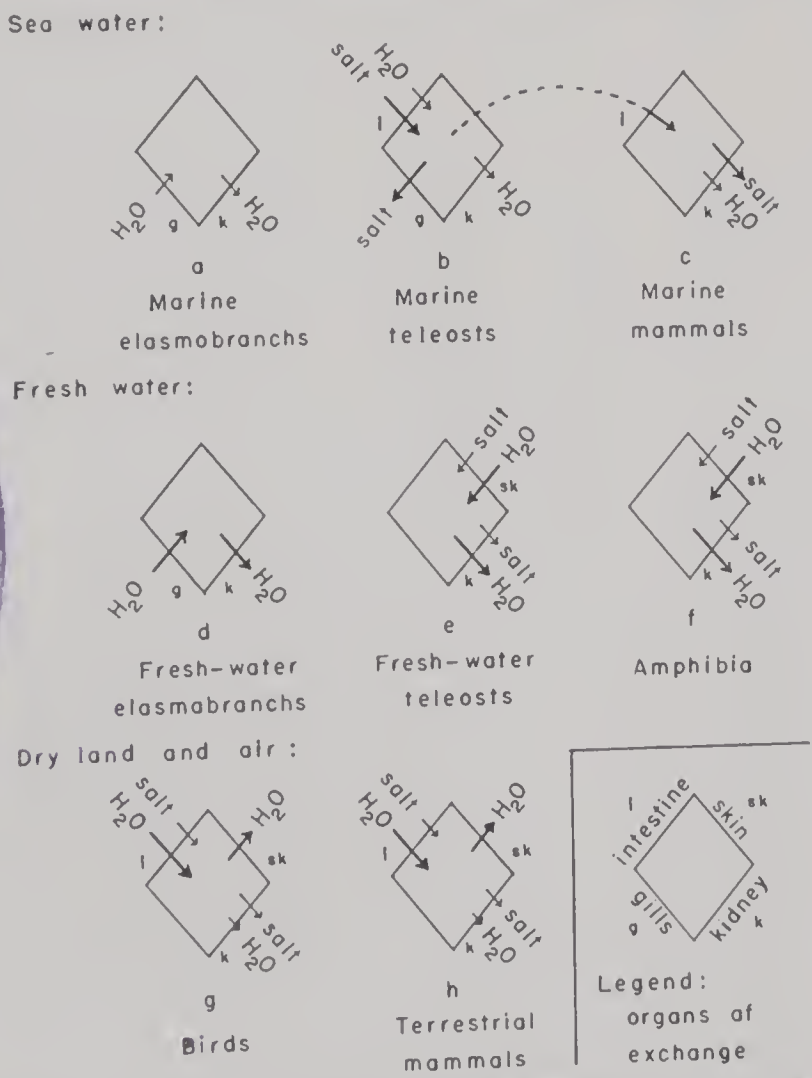
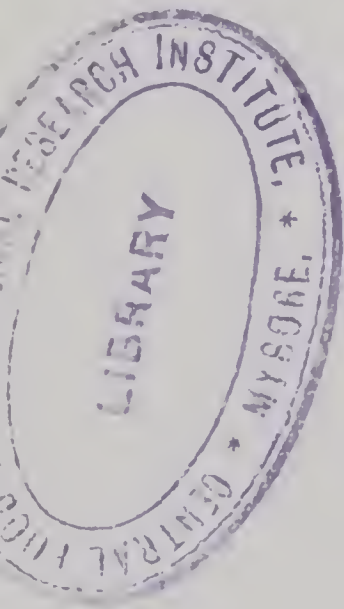


FIG. 2-5. SCHEMATIC REPRESENTATION OF THE OSMOREGULATORY MECHANISMS OF VARIOUS VERTEBRATE SPECIES IN MARINE, FRESH WATER, AND TERRESTRIAL HABITATS



ship of the water ingested in food and obtained from its oxidation to the water excreted by extra-renal, as well as renal, routes.

All marine mammals economize on water expenditure in relation to heat production since the loss of body heat directly by convection obviates the necessity for evaporation of water from the surface of the skin; sweat glands are absent. In addition, less water is required to saturate the smaller volumes of air in the lungs in the diving species where the increased pressure permits extraction of a greater percentage of oxygen from a given volume of air. The water content of feces is not greater than in terrestrial forms. The extra-renal water losses, therefore, are smaller in the marine mammals, and together with the renal expenditure do not exceed the total water available.

The marine mammal that has been most extensively studied is the seal (9d-h). The seal feeds on teleost fishes whose gills produce a body fluid hypotonic to the sea, and which body fluid then becomes available to the seal (fig. 2-5, c). On the other hand, many whales feed on invertebrates which are approximately isotonic with sea water: the baleen or whale-bone whales strain out plankton and the sperm-whales ingest cephalopods (squid, cuttlefish, etc.). The concentrating power of the kidney in the whales appears to be somewhat greater than in the seals, and the latter, when fed on a diet of clams, are less able to handle the extra salt (9e). The seal, however, in relation to his meals has a cyclic urine flow which may decrease to as little as 10 per cent of the post-prandial rate. This fall in volume flow is due to a decrease in glomerular filtration in all nephrons, and results in conservation of water at a time when the excretory solute load is low. This mechanism is probably related to the diving reflex described by Irving (9f) as resulting in diminished peripheral blood flow in diving mammals; asphyxia does produce a drop in rate of both filtration and excretion of water in the harbor seal (9g, h).

Irving *et al.* (9d) and Smith (9e) conclude that in the seal enough water is obtained by ingestion and oxidation of a diet of teleost fish to balance the losses of water outlined above. In 1250 grams of herring would be contained 1000 grams of water and another 121 would be yielded as the result of oxidation. Subtracting 106 grams plus 200 grams of water for vaporization and fecal excretion, respectively, 815 grams would be left for the renal excretion of the urea and salt from the herring. This would require a urinary concentration of 6.3 per cent urea and 1.4 per cent salt (freezing point  $-2.7^{\circ}\text{C}.$ ), which lies within the observed range. Krogh (3e) has extended this calculation to the whales which feed on invertebrates, with similar results. Fetcher (9c), however, has postulated that such whales may possess some other glandular mechanism for the selective excretion of salt. Certainly, in the lactating baleen whale the achievement of water balance remains an

enigma. Nevertheless, marine mammals do maintain water balance on the water available in food alone, although such balance is precarious at best in comparison with that of their terrestrial cousins on the banks of fresh-water streams.

Marine birds, such as the shearwater, the petrel, and the albatross, likewise live without access to fresh water. Their evaporative loss of water must be much higher than that of the immersed mammals over which they wing their way. It is presumed, therefore, that the minimal water excretion resulting from their uricotelic habitus is more than met by the preformed and metabolic water of their piscine diet. No adequate data, however, appear to be available.

**3. Desert animals,** like their marine counterparts, live in an environment where fresh water is at a premium. But unlike the marine habitat, the desert adds the stress of heat regulation to the problem of maintenance of water balance. The adaptations in animals and man to these environmental stresses have been reviewed extensively by Buxton, Dill, Adolf, the Schmidt-Nielsens, Smith, and others (10a-d, 3d). The physiological problems of man in the desert will be considered in greater detail in a subsequent section.

Despite the heat and the scarcity of water, many kinds of creatures live in the desert. Poikilothermic animals, whose body temperatures vary with that of the environment, have no need for water in the dissipation of heat; shade is their principal requirement. These include insects, amphibians, and reptiles. Insects pass through the larval stages below the surface of the ground during the driest time of the year, the adult forms appearing when some water is available in plants. Amphibians, the frogs and toads, cling to the humidity of subterranean burrows and come out only at night. The reptiles, lizards and snakes, obtain sufficient water from ingestion and oxidation of the insects on which they feed.

The homoiothermic, or warm-blooded mammals, cannot tolerate such wide variations in body temperature. Small desert mammals avoid the expenditure of water by burrowing in the ground during the heat of the day. Of these, the kangaroo rat appears to be the most completely adapted physiologically to the desert. As the Schmidt-Nielsens have shown (10d, e), this rodent can live on the metabolic water derived from eating dried seeds and other dry food, with no other source of water. Such maximum water economy is achieved by a greatly reduced water expenditure: evaporation from the body is less than half that of the white rat, and the kidney has the greatest concentrating ability known in any mammal. Distal tubular reabsorption is augmented by reabsorption of water in the collecting ducts, the bladder urine being concentrated to as much as 17 times the solute con-



centration in plasma.<sup>4</sup> The efficiency of this kidney is such that the kangaroo rat can tolerate well the ingestion of sea-water (10f) while the white rat (10g) and other mammals including man cannot (see below).

Other small rodents, such as the pack rat, cannot live on dried food alone but eat succulent vegetation and so acquire some preformed water. For all rodents the greater humidity underground is an important factor; it minimizes the rate of evaporation from the body and from moist food, and actually may increase the water content of dried food stored in the burrow. The small desert rodent does not store water in his body nor is he less susceptible to the physiologic effects of dehydration.

In contrast to the small mammals, the larger mammals in the desert with their smaller surface area per unit of body volume, gain less heat from the environment and so can afford to expend body water in the process of heat regulation. The common species, the gazelles, antelopes, elands, giraffes, and camels, are herbivores and, as ruminants, can digest hard grasses. The protein-poor diet results in a lower demand for urinary water in which nitrogen is excreted. Presumably these species can survive for a period of days on water of oxidation alone. The camel, especially, is noted for its ability to travel for long periods without water; eight days is usually the maximum period of water deprivation tolerated (10a) although Sven Hedin (10i), the Swedish explorer, reported travelling for almost four weeks with camels which received little or no water but whose diets were supplemented with oil.

The hump of the camel does not store water as such, but fat that is oxidized to water. Storage of water in the stomach by the camel has been reported, probably erroneously because of confusion with digestive juices. Camels are well insulated against heat gain by their fur. The degree of tolerance of heat load, which must be a major factor in determining the water balance of the species, is not known; much remains to be learned of the body fluid economy of the large desert mammals.<sup>5</sup>

The desert burro has been shown to have a sweating mechanism peculiarly well adapted to desert life (10b). This consists of the ability to lose heat in a sweat that is essentially salt-free. Dill and his associates observed a burro, deprived of water for 36 hours, to lose 7.4 kg. of weight during a 20-mile walk under the desert sun; at the end of this period the plasma chloride had risen 12.8 mEq. per liter. The burro then drank in five min-

<sup>4</sup> Sperber (10h) in his exhaustive study of the comparative anatomy of the mammalian kidney, found in rodents a close correlation between the elongation of the renal papilla (containing collecting ducts) and aridity of habitat.

<sup>5</sup> Drs. Knut and Bodil Schmidt-Nielsen and associates have recently returned from Algeria where they investigated this problem in the camel; at the time of writing, however, the results had not yet been reported (see *Fed Proc.* 14: 133-134, 1955).



utes 12.2 liters of water and the next morning, with no salt having been eaten, the plasma chlorides and weight were at the original normal level. When water is lost without salt, the loss is distributed over both extracellular and intracellular phases of the body fluids, and hence does not lead to the circulatory collapse consequent on depletion of extracellular fluid alone (10j, k).

Dog and man are poorly adapted to desert life, the dog because his evaporative heat loss is limited to the respiratory surfaces (panting), and man because his evaporative water loss is high and his sweat contains large amounts of extracellular electrolyte. Furthermore man, unlike the burro, is unable to replace his water deficit with water alone; if he does so, muscle cramps ensue. Men working in the desert or under conditions of great heat exhibit a slight acclimatization of a somewhat diminished salt concentration in sweat (10b, l) but seldom to a degree sufficient to render unnecessary the ingestion of supplementary sodium chloride.

#### **IV. Man and His Body Fluids under Environmental Extremes**

Men, as well as animals, are affected by extremes of climate and environment which place strains on mental and physical resources. We are concerned here with the effect of these stresses on the physiologic functioning of man's body in general and his body fluids in particular. What are the physiologic adaptations elicited and what disturbances occur when these adaptations break down? The answers to these questions come from many kinds of observations, including those made on races of men indigenous to various climates, and those made on man under controlled experimental conditions. The results of animal experiments also can be extrapolated to man if due consideration is given to species differences.

Environmental extremes of heat and cold are predominant factors in this discussion, since regulation of the body temperature is so closely bound up with the water balance of the body. In a cool climate with low humidity approximately 25 per cent of the metabolic heat to be dissipated from the body is transferred to the environment by evaporation of body water (not less than 0.8 liter per day per adult), the rest of the heat being transferred by radiation, conduction, and convection. In a hot environment the latter three types of transfer are reversed but vaporization from lungs and skin persists. In addition, sweating may be called into play to assist in heat expenditure, especially when a high humidity impedes vaporization. Under these circumstances maximum rates of water loss of between 3 and 4 liters per hour have been observed during exercise. It is obvious, therefore, that environmental conditioning of body heat transfers may have a profound effect on the body fluids. Physiologic literature reviewing this subject has

already been cited (10b, d); to these should be added the monograph on heat regulation edited by Newburgh (11a).

*A. Cold: The Circumpolar Regions and the Winter Sea*

**1. Ecology.** The cold areas of the world which are inhabited include the Arctic regions of the Old and New Worlds, Tierra del Fuego near the Antarctic, and the high plateaus of Tibet and the Andes. The cultural and physical adaptation of the inhabitants of these areas has been described in detail by Wulsin (11b). Eskimos and Siberian tribes have evolved extremely efficient types of clothing and housing for the conservation of body heat; Stefanssen (11c) states that the Eskimo carries about his own temperate climate inside his fur clothes. These peoples, therefore, probably exhibit no great abnormality of the body fluids. On the other hand, the inhabitants of Tierra del Fuego live in varying degrees of nakedness in an extremely wet, cold climate. Darwin (11d) describes an apparently unconcerned and completely unclothed woman of the Yahgan tribe, nursing a naked baby, on both of whom the sleet melted as it fell. Natives of this tribe perspired profusely when sitting at a distance from the camp fire which barely warmed the Europeans. The aboriginal Australian Bushman sleeps naked on the ground in freezing temperatures with only a small fire to warm him. Both of these peoples must have physiological adaptations for body heat conservation, but only on the latter have quantitative observations been made. Hicks and associates (11e) found no change in basal metabolic rate, but rather an increased ability to localize peripheral vasoconstriction and a decreased threshold to the sensation of cold. Coon (11f) in his discussion of the effect of climate on racial characteristics, finds that, in general, peoples living in cold climates, in addition to much subcutaneous fat about the exposed face, wrists and ankles, have small hands and feet and short fingers and toes. Such characteristics diminish the evaporative water and heat loss from those areas of the body, and with peripheral vasoconstriction the arm becomes "an insulator in depth." The opposite is true of peoples native to hot climates who have little subcutaneous fat and long arms and fingers with a large surface area relative to the tissue volume, circumstances making for efficient heat loss.

**2. Experimental** evidence of the effect of cold on heat regulation and on the body fluids has been reviewed by Speakman (11g). Acute exposure to cold results first in reduction of heat loss by peripheral vasoconstriction and then in increased heat production by shivering. Chronic exposure to cold does not lead to large changes in the basal metabolic rate; the adaptations achieved are circulatory. In experimental hypothermia, diminution in blood volume has been observed (11h), and internal shifts of water into



cells have been calculated to occur (11i, j). Magnesium metabolism has been implicated. Serum magnesium levels may be elevated in hibernating animals (11k) and in experimentally cooled animals (11l, m) and lowered in man acclimatized to cold (11n); it is possible that magnesium levels are related to sensitivity of hypothalamic heat regulating centers. More recently, interest in the physiologic response to cold has been renewed by the development of the use of hypothermia as an anesthetic procedure for cardiac surgery. But, in general, it can be concluded that disturbances in man's body fluids as the result of exposure to climatic cold are not of great clinical importance.

### *B. Heat: The Desert, the Jungle, and the Tropical Sea*

Extremes of heat place a far greater strain on the economy of man's body fluids than do extremes of cold. The reason for this is obvious: in the hot environment a much larger water-turnover is required to sustain evaporative heat loss. Many clinical and experimental studies have been made of the physiologic response to heat; the most complete reviews of the problem are those of Dill (10b) and of Adolf and associates (10c).

**1. Ecology.** Man has inhabited the hot, wet areas of the world; the jungles, and the islands in tropical seas, and the hot, dry areas; the deserts that spread around the world on the Tropics of Cancer and Capricorn. Civilizations and advanced cultures have flourished in both wet and dry heat, such as the Javanese and Mayan in the former, and Egyptian, Babylonian, and Islamic in the latter. In all of these cultures men learned to protect themselves with suitable clothing and housing against the uptake of radiant and convective heat, and to foster evaporative heat loss by ventilation, bare skin, and removal of body hair (11b). As pointed out above, the peoples of hot climates tend to deposit little subcutaneous fat and have long arms and slender fingers which permit greater heat loss per unit of tissue volume (11f). The *sine qua non* of their existence is the availability of ample supplies of water.

**2. Experimental** results of physiologic studies of man in hot environments have been reviewed in detail elsewhere (10c, 12a). If hydration is adequate, blood and plasma volumes are increased and the peripheral circulation becomes more efficient in its transfer of heat from the interior of the body to the surface for loss by evaporation (11h, 12a). Sweating begins when the humidity is low and the ambient temperature is above 29°C. for the clothed, and 31°C. for the nude, subject. In more humid environments sweating starts sooner. The rate of sweating is conditioned by both skin and internal temperatures, and may reach values of 0.5 liters per hour (resting in the shade) to over 3 liters per hour during exercise in the sun (12b, c). Acclimatization results in increased sweating at lower



body temperatures (12a-e). High rates of water loss in sweating, if not replaced by ingested water, quickly lead to dehydration.

Sweat is a hypotonic solution of extracellular electrolytes, chiefly sodium and chloride. Depletion of these ions leads to circulatory collapse; replacement of sweat with water without salt produces muscle cramps (12f, g). Ladell and associates (12b) found that the common type of heat exhaustion in British troops in the Middle East was essentially a salt depletion syndrome. Acclimatization to heat involves not only increase in rates of sweating but decrease in concentration of salt in the sweat (10b, 1); clear evidence has been adduced that adrenocortical hormones are one factor in the rate of salt loss through sweat glands (12h-j). However, man does not adapt his sweating to the extent of sweating salt-free water like the burro, and therefore should supplement his drinking water with sodium chloride when sweating profusely and drinking freely in a hot environment (12k).

### *C. Thirsting States: Water Deprivation, Sea Water Ingestion*

Man is in a thirsting state when his supply of water is insufficient to meet his needs. Since his need for water is greater under conditions of heat, this state usually occurs in the desert or on the tropical sea. In either of these hot environments water deprivation limits survival; in the cold environment (as on the winter sea) water deprivation is of less consequence since death from the cold long precedes death from desiccation.

There have been many vivid descriptions of the ordeal of thirst in the desert including Sven Hedin's (10i) account of his harrowing march across the Takla-makan Desert in Sinkiang, King's (13a) report on a troop of cavalymen lost without water in the Colorado desert, and that of McGee (13b). The latter author's description of the progressive stages of such dehydration is graphic: "clamorous, cotton-mouth, swollen-tongue, shriveled-tongue, and blood-sweat". The most succinct and classic description of thirst at sea is that of the Ancient Mariner (13c).

When approximately 12 per cent of the body water has been lost, the victim can no longer swallow; when 15 to 25 per cent has been lost, death ensues (10c). In great heat, death comes much more quickly and is probably due to an explosive rise in deep body temperature; in cooler environments, death from dehydration probably results from circulatory failure. Survival time in either case depends upon the relation of exercise to ambient temperature. Adolf estimates that a man walking only at night may survive 18 days without water when the daily mean and maximal air temperatures are 60° and 70°F., respectively; when the same temperatures are 98° and 115°F. his probable survival time is 2 days.

The effects of dehydration on the body fluids are discussed in detail in Chapter 6, and therefore are mentioned only briefly here. Pure water

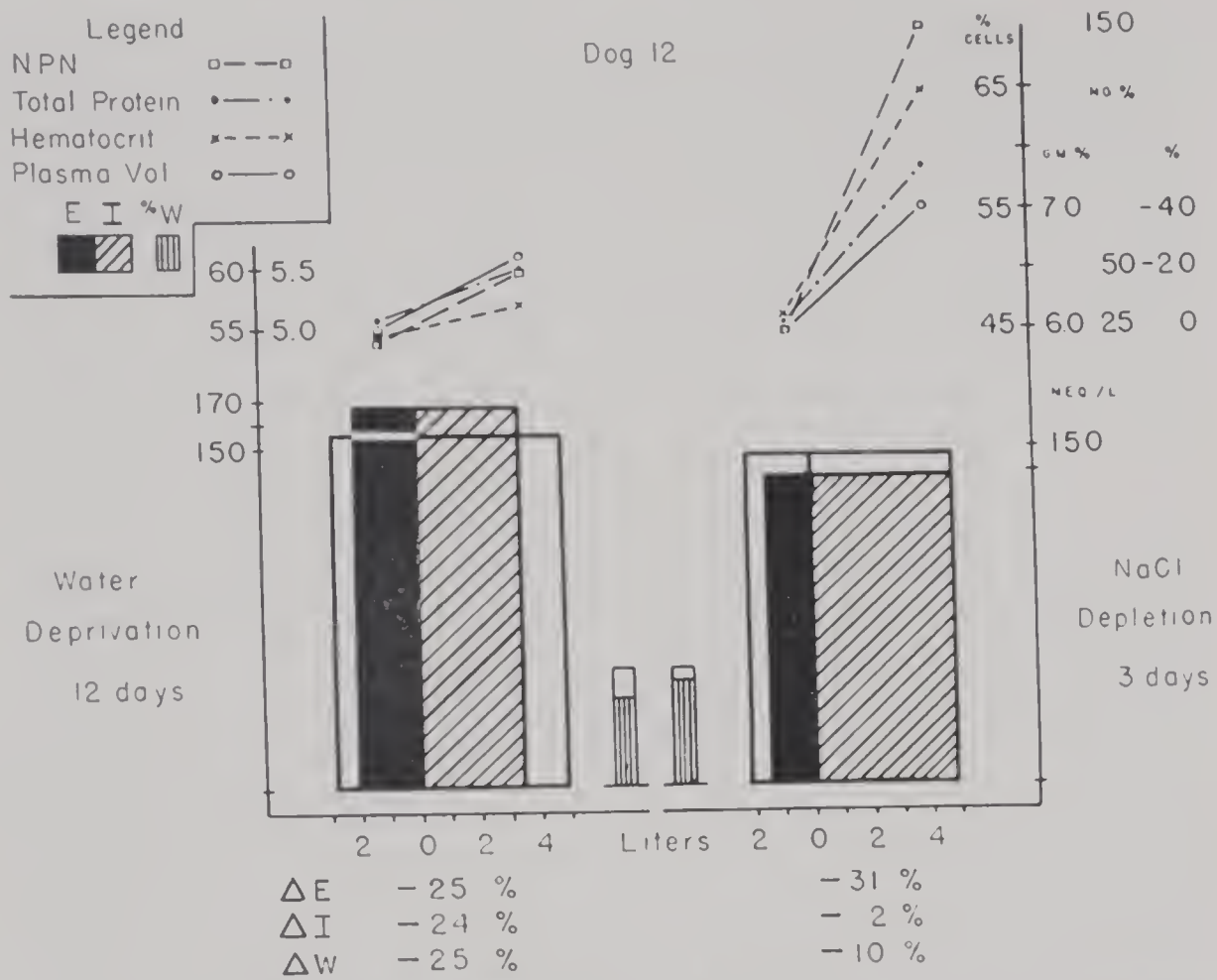


FIG. 2-6. COMPARISON OF THE EFFECTS ON THE BODY FLUIDS AND PLASMA VOLUMES OF WATER DEPRIVATION AND SODIUM CHLORIDE DEPLETION IN THE DOG

Cation concentrations are plotted along the ordinates; fluid volumes, along the abscissae. The initial state is shown in outline in each figure; the solid and cross-hatched areas represent the extracellular and intracellular fluids, respectively. The small vertically-lined columns represent change in total water. The figures below the diagram are cumulative percentage changes in extracellular ( $\Delta E$ ), intracellular ( $\Delta I$ ), and total water ( $\Delta W$ ). Plasma volumes are given in per cent of initial values.

The left-hand diagram presents the effects of dehydration due to 12 days of water deprivation: both fluid phases are depleted of water to an equal extent. The right-hand diagram presents the effect of sodium chloride withdrawal: the extracellular phase alone is depleted and the drop in plasma volume is much greater than that produced in water deprivation. (From Hopper *et al.* (10k).)

deprivation results in dehydration of both extracellular and intracellular phases of body water, whereas sodium depletion results in a drop in extracellular fluid volume alone (10j) (fig. 2-6). The latter is associated with more profound circulatory failure (10k, 14a). The salt lost in sweat leads to circulatory collapse but since the water loss is relatively greater than the salt loss, both phases of body water are depleted (14b, c). Cellular dehydration appears to be a prime factor in thirst.

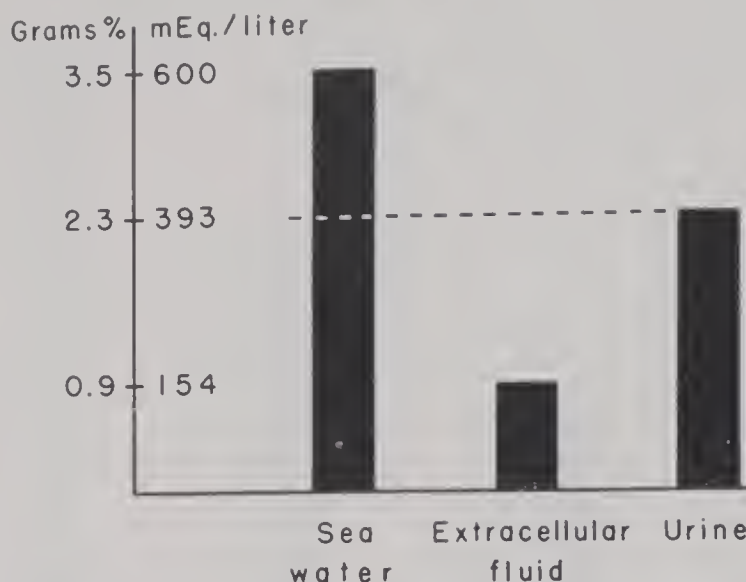


FIG. 2-7. THE CONCENTRATIONS OF TOTAL CATION AND SODIUM IN SEA WATER, EXTRACELLULAR FLUID, AND MAXIMALLY CONCENTRATED HUMAN URINE

The concentrations are calculated as grams per cent sodium chloride and as mM. per liter. The total height of each column represents total cation concentration, the solid portion of the columns that of sodium.

The height of the urine column indicates maximal concentration of sodium in urine under conditions of water deprivation and ingestion of sea water (15f). The difference in height between the solid portions of the sea water and the urine columns indicates the sodium which, when ingested in sea water, either must be retained or must have additional water for its excretion. (From Elkinton and Winkler (15b).)

The man castaway at sea without a supply of fresh water would appear to be in just as precarious, and in a more tantalizing, situation than the man lost in the desert. He cannot meet his needs alone from the limitless waters on which he floats; ingestion of undiluted sea water only hastens death (15a, b). Given kidneys which cannot concentrate urine to the osmolarity of the sea water taken in (fig. 2-7), body water is sacrificed to excrete extra salt and retained sodium salts exacerbate cellular dehydration (fig. 2-8). Experimentally, intracellular dehydration is associated with central nervous system dysfunction and respiratory paralysis (15c). In most accounts of castaways who have drunk undiluted sea water, the fatal course has been characterized by delirium and coma. Gastro-intestinal intolerance of the magnesium and sulfate in the sea water is also a limiting factor.

The castaway at sea has a better chance of mitigating his negative water balance than does the man lost in the desert. If the sea and air are not too cold, he may minimize the evaporative loss of body water by staying in the shade (if available) and by substituting sea water to cool the surface of his skin (15d, 10c) (fig. 2-9). In addition he can supplement his water



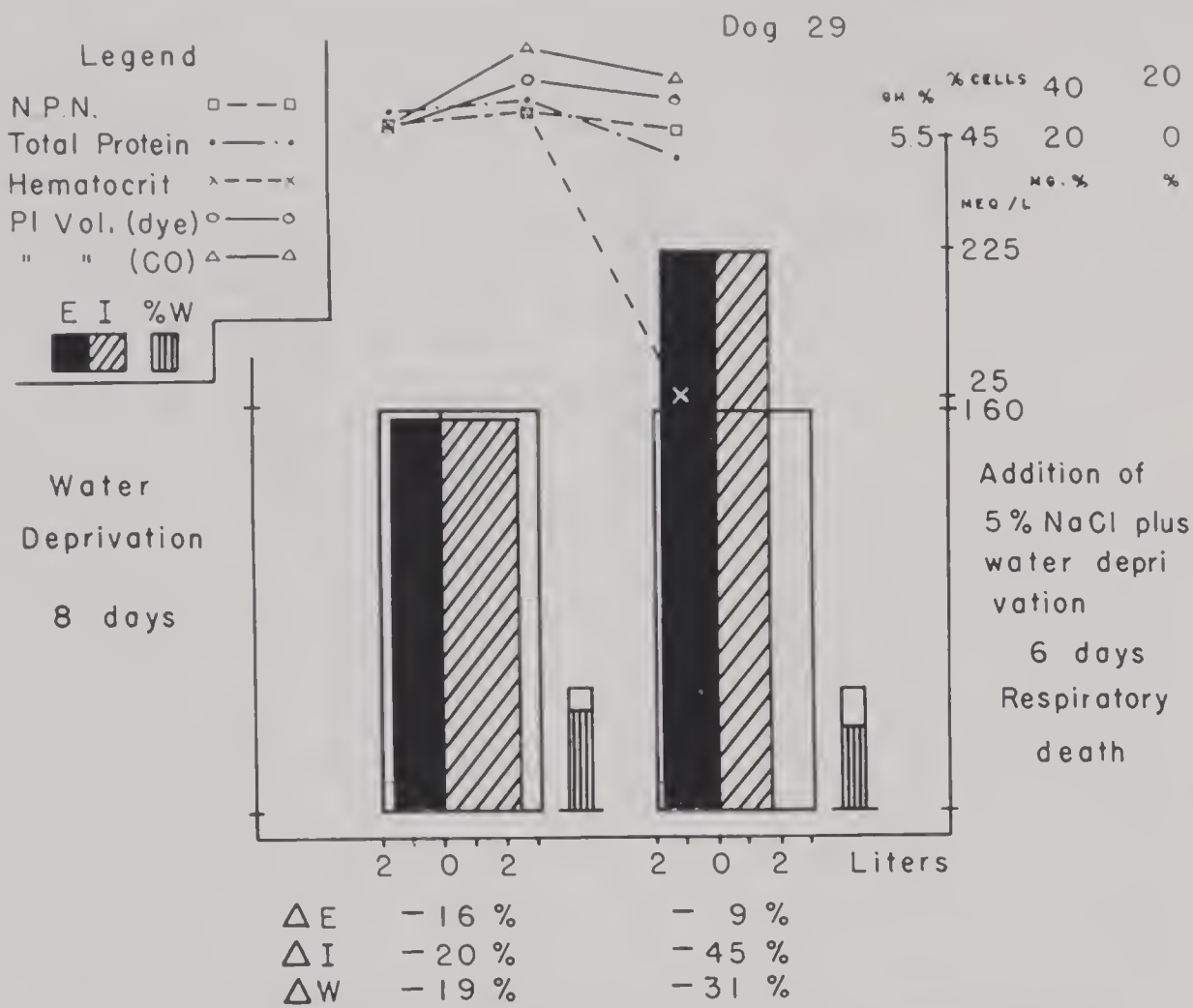


FIG. 2-8. THE EFFECT ON THE BODY FLUIDS OF EXPERIMENTAL WATER DEPRIVATION FOLLOWED BY INJECTION OF HYPERTONIC SODIUM CHLORIDE SOLUTION IN AMOUNTS SIMULATING THE INGESTION OF SEA WATER

Data are plotted as in figure 2-6. The figure at the left represents the state after eight days' deprivation of food and water, the figure at the right, the state after six more days of repeated injections of hypertonic saline solution.

Simple deprivation of food and water caused both phases to contract equally. Injection of hypertonic saline solution at this time resulted in further loss of body water and in some retention of sodium chloride. As a result of this salt retention, the extracellular fluid re-expanded at the expense of the intracellular fluid in spite of the increased total water depletion. Ultimately death occurred from respiratory failure associated with extreme depletion of intracellular water. Plasma volume and circulation were maintained throughout. (From Elkinton and Winkler (15b) )

supply by diluting sea water, volume for volume, with whatever meager amounts of fresh water that he may have, since the kidney can handle the extra salt in the less concentrated solution (15d-f). His best chance of adding to his supply of potable water lies in the catchment of rain; there are few areas of the world's oceans where rain does not fall periodically.

The ingestion of teleost fish also has been suggested as a source of water

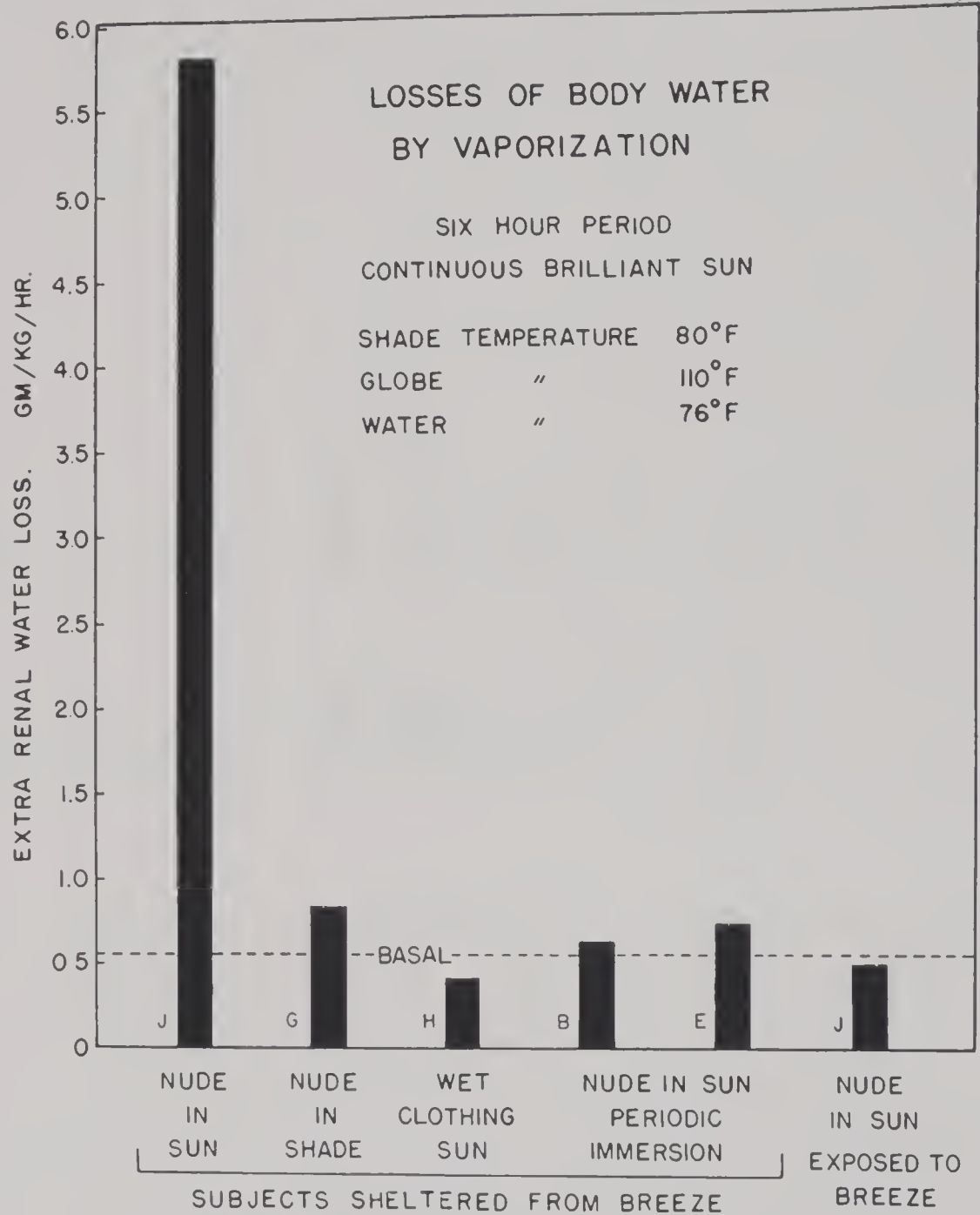


FIG. 2-9. EXPERIMENTAL STUDY OF THE LOSS OF BODY WATER BY VAPORIZATION FROM CASTAWAYS IN WARM SEAS

The extra-renal water loss, when in the sun and sheltered from the breeze, is greatest when nude and smallest when in wet clothing. Similar conservation of water during heat expenditure is accomplished in the nude subject in the sun by exposure to a breeze. (From Gamble (15d).)

for the castaway man (as it is for the seal). The human kidney, however, is less efficient than that of the seal, for all of the water in the fish is required to excrete the extra urea and electrolytes (15g) (fig. 2-10); the only advantage gained is that of the calories. For the same reason, emergency rations should avoid protein and salt, and are best made up of carbohy-

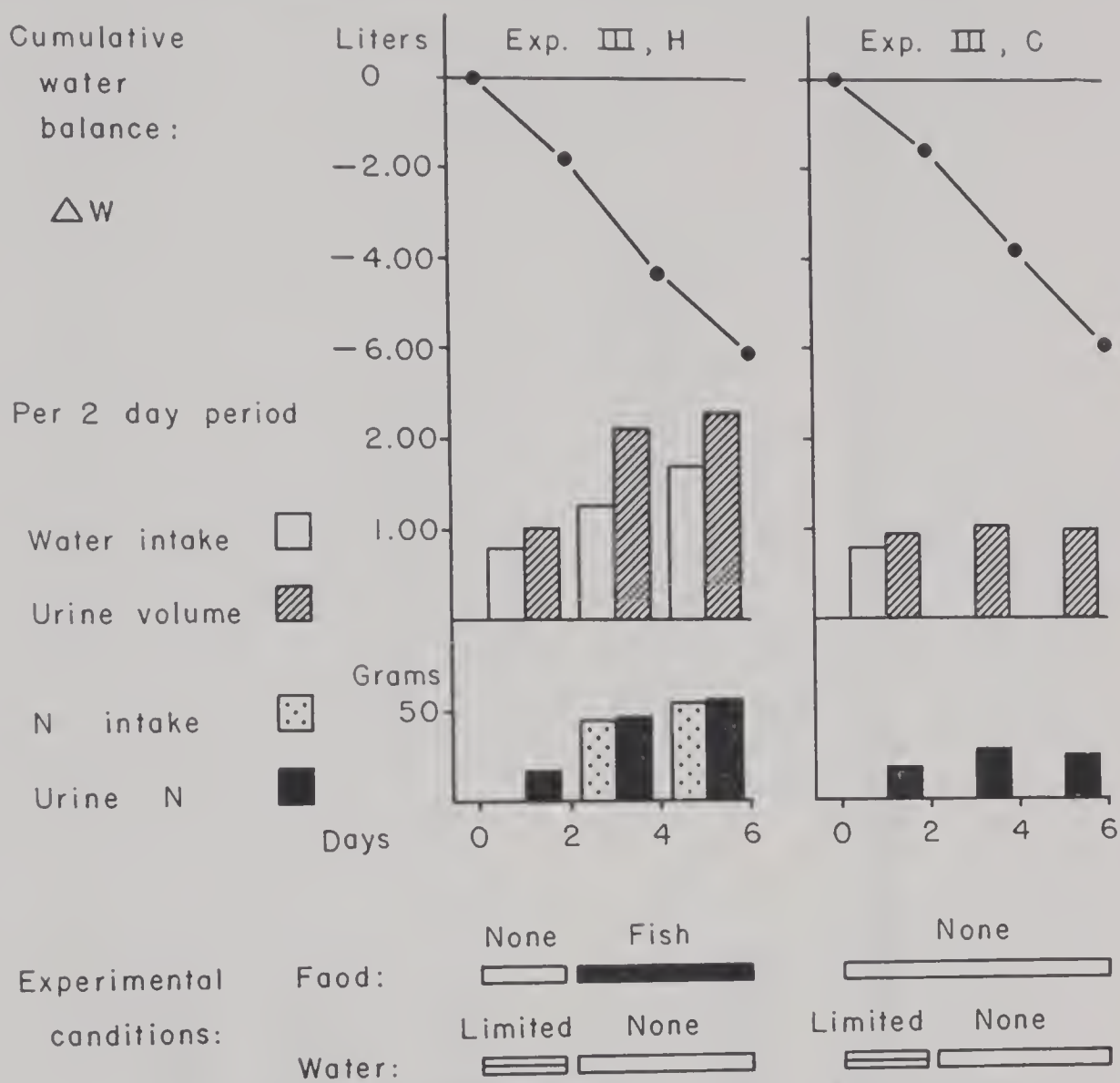


FIG. 2-10. FAILURE OF THE INGESTION OF FISH TO MITIGATE THE DEHYDRATION OF A SUBJECT DEPRIVED OF WATER

Subject III-H ate fish while III-C served as a control. Water derived from the fish was not retained by subject III-H, so that both subjects lost water at approximately the same rate. Failure of water retention was apparently due to the greatly increased production of nonprotein nitrogen, with consequent increase in the volume of urine used in its excretion. However, the ingestion of the fish did prevent a severely negative balance of nitrogen. (From Winkler *et al.* (15g).)

drates and fats (see figure 6-4); pemmican, the standby of the wilderness explorer, is not for the thirsty man at sea.

*D. High Altitude, Deep Sea Diving*

The physiologic effects of these two environmental extremes are complex and involve primarily the processes of gas exchange. In respect to the body fluids only two effects of high altitude will be mentioned. Hyperventilation due to low oxygen pressures may lead to carbon dioxide deficit and respira-



tory alkalosis. Chronically, low oxygen pressure may produce an increase in circulating red-cell mass, as found in the acclimatized subject. Dill reviews the literature on high altitude physiology (10b).

The deep sea diver travels between the Scylla of oxygen poisoning and the Charybdis of nitrogen bends. For the moment he represents the frontier and end of our environmental journey.

**SUMMARY:** Sodium and potassium are distributed differentially on the geochemical as well as on the biological level, the former accruing to the sea and to extracellular fluids, and the latter to the soil and to cells. The predominance of sodium in vertebrate extracellular fluid is a heritage of the marine origin of living organisms, but in response to the stimuli of varying habitats, the precise character of the internal environment has been greatly modified as the organs of exchange with the external world (especially the kidney) have evolved over geological time. Today, living creatures and their body fluids are adapted to open oceans, inland waters, dry land, and the sky above. Many of these domains are shared by man, but he is limited in his adaptation to environmental extremes. On these frontiers of heat, cold, altitude, and salinity, man and the integrity of his body fluids are strained, and he survives only by his own foresight and provision for his physiologic needs.

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"It is hard to empty the well of Truth with a leaky bucket."

Sir Arthur Eddington in *The Nature of The Physical World*

## Chapter 3

### METHODS OF STUDYING BODY FLUID DISTRIBUTION

In the first chapter we have attempted to present a concise over-all concept of body fluid dynamics. Such a concept has been developed through employment of a wide variety of experimental technics and methods. Many of these methods are in active use today and are undergoing further refinement as tools for clinical and physiological investigation. Some are more directly applicable than others to the study of the sick patient, but all have contributed to a better understanding of the processes of disease as well as of those of normal function. For this reason, if the serious student is to make adequate use of the concepts presented in the first chapter, he needs to have some knowledge of the methods by which they have been developed.

Methods of studying the composition and exchanges of the fluid parts of the body first may be divided into those involving isolated tissues and those concerned with the intact organism. In the former category the studies may consist on one hand of chemical analysis of various tissues which have ceased to function, or, on the other, of *in vitro* observations of dynamic processes occurring in isolated but surviving or living tissues. Observations in the intact organism, animal or man, include methods of determining the volume of distribution or dilution of an administered solute or isotope, of measuring flux or turnover with tagged molecules or ions, of determining changes in body composition by comparing intake with output using the balance technic, and of observing regional exchanges of fluid. Finally, by combination of various of these methods it is possible to make a correlated chemical dissection of the body and its fluids and so to enhance our knowledge of the structure and function of the normal and the diseased organism.

#### I. Studies of Isolated Systems and Tissues

##### A. Blood or Tissue Analyses

Analyses of blood, serum or plasma have long been used as indices of the concentrations of body constituents in these particular fluid phases. More



recently this same technic has been employed in studying the composition of the various tissues of the body since they also can be analyzed for their content of water and electrolytes. The content of water and solids is determined by weighing the specimen before and after a standard drying procedure. The residue is then analyzed for fat and nitrogen and, after wet or dry ashing, for electrolytes by the usual chemical methods. If the simultaneous concentrations of electrolytes in the extracellular portion are known, that is, simultaneous in time with the taking of the specimen, certain values can be derived with respect to the phase distribution of water and electrolytes in the tissue. Such a derivation is based on the assumption that one of the constituents, measured as to amount and concentration, is confined to the extracellular phase. Taking chloride ion to be such a substance, calculations of the proportions of solids and intracellular and extracellular fluid phases have been made for all the major tissues of the mammalian body. Body composition of total desiccated carcasses has been determined in this way for animals (1a) (see fig. 1-3), and for man (1b).

It is recognized that chloride is not entirely confined to the extracellular fluid and hence cannot be used as the basis for calculating the true extracellular fluid. Other substances, such as inulin, have been infused prior to the obtaining of the tissue specimen, and have then been utilized for the reference point for the extracellular phase. However, the validity of the inulin space as a measure of the extracellular fluid has been questioned and to date this problem of an adequate substance for extracellular fluid measurement has not been completely solved. In any case, in tissues such as skeletal muscle, phase calculations based on chloride have given much useful information.

Since skeletal muscle is the most important single tissue in terms of bulk (40 to 50 per cent of the body weight), it is usually considered to give the maximum amount of information about the state of fluid distribution in the body. Some data on the content of water and electrolytes of skeletal muscle, as well as values for phase distribution as derived from these observed data, are given in table 3-I and illustrated in figure 3-1 (2a-c). It should be recognized that values so determined at any given time represent a measurement that is dynamic only in the sense that changes have been induced prior to the time of taking the specimen.

The analyses of the constituents of any tissue require some point of reference to make them meaningful. Quantitation per unit weight of the whole tissue specimen has been a common practice in the past. In respect to muscle analyses, however, it was found that such quantitation must be corrected for the variable amount of fat in the tissue. Hastings and Eichelberger (2a) therefore expressed their findings in *units per kilogram of fat-free wet muscle*. However, since the extracellular and intracellular fluid phases may vary independently of each other as well as of the solid content of the tissue, Darrow, Harrison,

TABLE 3-I.

WATER AND ELECTROLYTE CONTENT OF SKELETAL MUSCLE OF NORMAL DOGS				
I. PER KILOGRAM FAT-FREE WET MUSCLE				
				A <sup>*</sup> B <sup>#</sup>
Total muscle	chloride	mEq.	21.5	20.7
" "	sodium	"	32.4	29.2
" "	potassium	"	82.1	93.7
" "	water	gm.	765	772
Extracellular	phase	"	174	169
Intracellular	"	"	826	831
"	water	"	593	605
"	sodium	mEq.	7.2	3.9
"	potassium	"	81.4	92.9
II. PER 100 GRAMS FAT-FREE SOLIDS				
Total muscle	chloride	mEq.	9.2	9.1
" "	sodium	"	13.8	12.8
" "	potassium	"	35.0	41.1
" "	water	gm.	326	339
" "	solids	"	100	100
Extracellular	water	"	73	73
Intracellular	"	"	252	266
"	sodium	mEq.	3.1	1.7
"	potassium	"	34.6	40.8

\* 20 normal dogs of Hastings and Eichelberger (2a)

# 4 normal dogs of Darrow, Harrison and Taffel (2b)

and Taffel (2b) presented their data as muscle water and electrolyte in terms of *units per 100 grams of fat-free solids*. Of course, each of these two methods of expressing such data can be readily converted into the other. Recently, Lijlenthal and co-workers (2d, e) have proposed that a more accurate reference point would be the noncollagenous nitrogen of the tissue. This fraction of the total nitrogen is that of the intracellular protein and its use as a reference point eliminates variability due to connective tissue in the specimen.

Given the analytical values for water and electrolytes in serum and in the fat-free muscle, the phase data may be derived in *units per kilogram of fat-free wet muscle*. This derivation according to the method of Hastings and Eichelberger (2a) is summarized as follows, substituting E and I as symbols for the extracellular and intracellular phases, respectively:

$$E = \frac{Cl_M \times 0.95 \times 1000}{Cl_{sw}}$$

(1)

where  $Cl_M$  represents the chloride in muscle in milliequivalents per kilogram of fat-free wet muscle,  $Cl_{sw}$  the concentration in serum water in milliequivalents per liter and 0.95 is the Gibbs-Donnan factor. From the value for E, in grams, that of the intracellular phase, I, in grams, is calculated:

$$I = 1000 - E$$

(2)

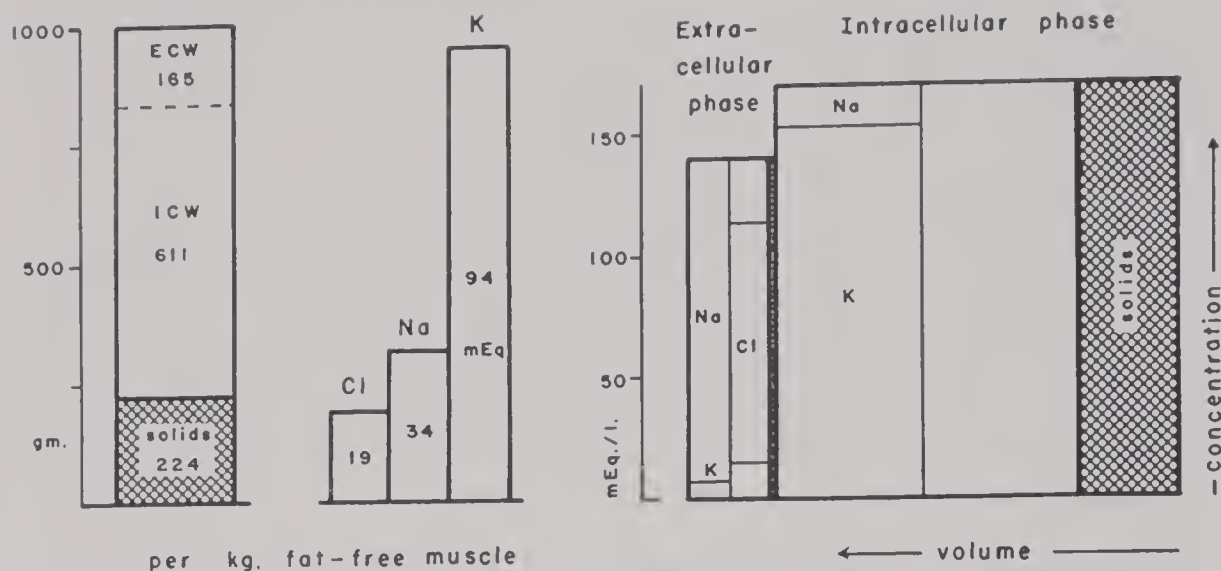


FIG. 3-1. WATER AND ELECTROLYTE COMPOSITION OF HUMAN FAT-FREE SKELETAL MUSCLE

The content per kilogram of wet muscle is shown on the left. On the right the composition is depicted in terms of volume of extracellular and intracellular phases along the abscissa and of concentration along the ordinate. Ionic patterns are superimposed on the aqueous portion of each phase (cf. fig. 3-6). (Data are from Talso *et al.* (2c).)

The intracellular water,  $H_2O_I$ , is then calculated:

$$H_2O_I = H_2O_M - H_2O_E \quad (3)$$

where

$$H_2O_M = \text{gm. water per kg. muscle}$$

$$H_2O_E = \text{gm. extracellular water per kg. muscle}$$

$$= 0.99 \times E$$

$$\text{assuming 1\% of the phase to be solids} \quad (4)$$

From the concentration of sodium and potassium in serum, the amounts of these electrolytes in the two phases may be calculated, using a Gibbs-Donnan factor of 0.95:

$$Na_E = H_2O_E \times 0.95 [Na]_{sw} \quad (5)$$

$$Na_I = Na_M - Na_E \quad (6)$$

$$K_E = H_2O_E \times 0.95 [K]_{sw} \quad (7)$$

$$K_I = K_M - K_E \quad (8)$$

where  $[Na]_{sw}$  and  $[K]_{sw}$  represent the concentration of these ions in serum water.

The above values for the phase distribution of water and electrolytes may be recalculated, as Darrow *et al.* (2b) have suggested, in terms of units per 100



grams of fat-free solids, by multiplying by the factor:

$$\frac{100}{1000 - H_2O_M}$$

Manery *et al.*, Wilde, and Yannet and Darrow have shown that about one milliequivalent of chloride per 100 grams fat-free solids of muscle is not in free equilibrium with ultrafiltrate of serum (3a-c). The last authors suggest that muscle chloride content should be corrected by subtracting such a fraction before employing it to calculate the extracellular phase. Comparison of the effects of basing this calculation on such a corrected chloride space with the results of the use of the total chloride or inulin spaces has been made for human muscle by Mokotoff, Ross, and Leiter (3d).

Such analyses of skeletal muscle have been applied to the study of many experimental and clinical conditions. The former include exercise, aging, sodium depletion, potassium depletion, adrenocortical insufficiency, administration of desoxycorticosterone, alkalosis, acidosis, and shock following burns or hemorrhage (3c, 4a-r). Clinical states in which such analyses of muscle have been made include, among others, metabolic alkalosis and acidosis, nephrosis, congestive heart failure and hypertension (2e, 3d, 5a-f). In all these conditions, knowledge of the water and electrolyte distribution in individual tissues has contributed greatly to the understanding of the fluid dynamics in the whole organism. The subject of tissue electrolytes recently has been thoroughly reviewed by Manery (6).

### *B. Tissue Metabolism in vitro*

When tissue is removed from a living body or from a body that has just ceased to live as an integrated organism, the tissue does not immediately die. If optimal conditions of nourishment, osmolar environment, and oxygenation are provided to a tissue whose integrity has not been grossly disturbed, its metabolic processes may be maintained for a prolonged period. From such an experimental preparation much can be learned of the fluid dynamics by observing the effects of varying environmental conditions, such as temperature, oxygenation, and the presence of substrates for, or inhibitors of, enzymatic reactions within the cells.

Blood is an individual tissue that can be readily studied in this manner with respect to the dynamics of the fluid exchanges between its extracellular phase (plasma) and its intracellular phase (erythrocytes). Blood is unique among the tissues of the body in that it is possible to separate almost completely the two phases for chemical analysis. Study of the exchanges of water and electrolytes between red cells and plasma under various conditions of aerobic and anaerobic metabolism contributed some of the earliest and most detailed knowledge of such exchanges between a cell and

its surrounding medium. Water was shown to shift across the cell membrane in accordance with the relative osmotic pressures of the two phases (7a). As indicated in chapter 1, the differential distribution of electrolytes between the two phases depends on metabolic processes within the cells.

Exchanges of solutes in other living tissues have been studied in the Warburg apparatus. Slices of living tissues such as the renal cortex, the liver, or the diaphragm of the rat are placed in this apparatus under conditions that permit their cells to function. By study of the bathing fluids and of the tissues it is then possible to learn something of the shifts of electrolytes into and out of the tissue as they are affected by the conditioned cellular reactions. In figure 3-2 is illustrated the influence of cellular oxidation on the movement of potassium into tissue cells. Three tissues, human blood, rat renal cortex, and rat diaphragm are being investigated as to three metabolic variables: glucose substrate, acetate substrate, and oxygen (7b-d). Each of these substances enhances the movement of potassium against, or prevents movement with, the concentration gradient, which is evidence for the dependence of the differential distribution of potassium on cellular metabolism. Similar experiments have been performed with many

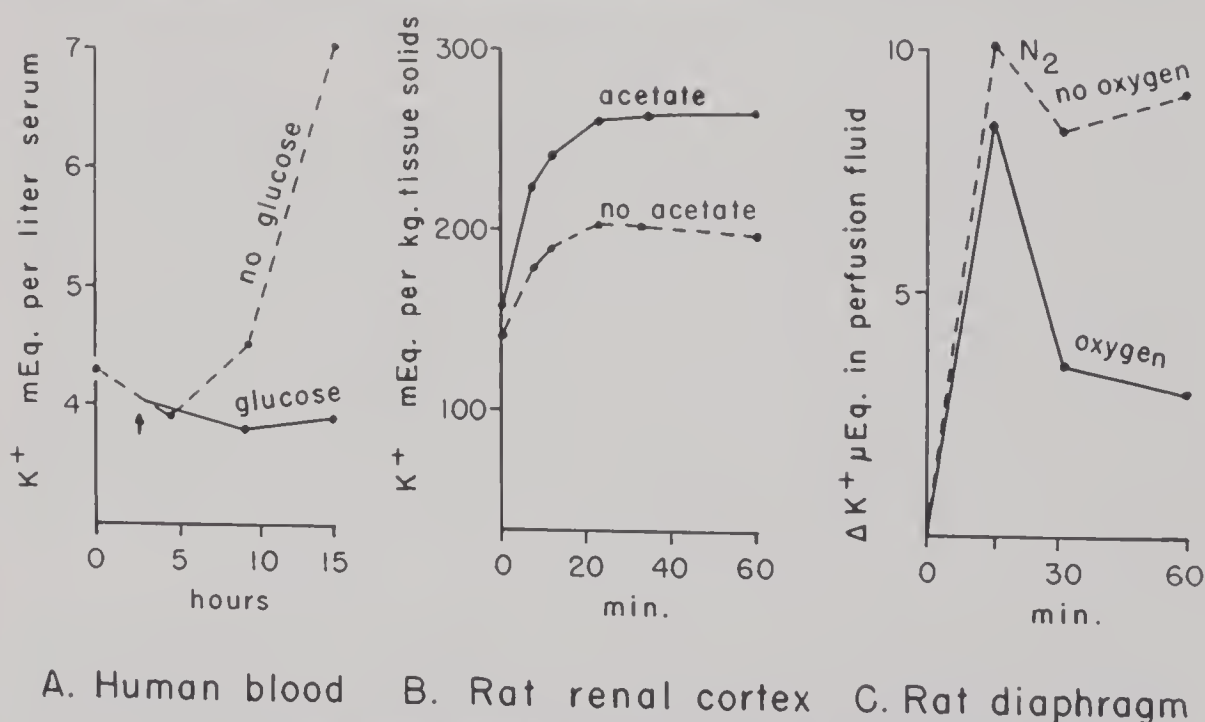


FIG. 3-2. THE EFFECT OF METABOLIC VARIABLES ON POTASSIUM TRANSFERS IN SURVIVING TISSUES *in vitro*

A indicates the inhibition by glucose substrate of potassium transfers out of human erythrocytes into plasma. (From the data of Danowski (7b).) B demonstrates the enhancement of potassium transfer into rat renal cortex by acetate substrate. (From the data of Mudge (7c).) C indicates the decrease in the rate of potassium loss from cells of the rat diaphragm under the influence of oxygen. (From unpublished studies by Squires and Marsh (7d).)

other variables including other substrates, low temperatures, and enzyme inhibitors such as cyanide and fluoride (7c).

## II. Studies in the Intact Organism

There are a variety of ways in which the distribution of body fluids can be studied in the intact organism. One of these is to measure the various fluid compartments by determining the *apparent volume of distribution* or the *dilution* of any added solute which has distributed through that particular phase or compartment. This is an *absolute* measurement. Another method is to calculate *changes* in the several compartments, and in their constituents, by the *balance technic*, which is based on quantitation of intake and output of the body fluid constituents in question.

### A. The Dilution Technic, i.e., the Apparent Volume of Distribution

This technic depends upon the relationship of the concentration of a solute in a solution to the volume of the solution and the amount of the solute. Thus, if the amount of a solute,  $A$ , and its concentration,  $C$ , in a solution, are known, the volume,  $V$ , of the solution can be calculated from the equation:

$$V = A/C \quad (9)$$

The conditions necessary for such a measurement are the following: 1) that the solute injected be evenly distributed through the body fluid compartment being measured, with no transfer of the solute into another fluid phase where it is present at a different concentration; 2) that a representative sampling of the concentration of the solute can be made, usually from the blood serum or plasma; 3) that the amount of solute retained in the body can be accurately determined from the amount injected, corrected for the amount excreted or destroyed by any route. Deviations from these conditions require careful consideration in the application of the technic and in the interpretation of the results.

The principal methods of application of the *volume of distribution technic* are illustrated in figure 3-3. One method is to administer a *single injection* of the solute. In figure 3-3, A is shown the curve for the serum concentration of an injected substance plotted against time. Following the initial period of mixing, such a curve, when plotted semilogarithmically, is a straight line, whose slope is determined by the rate at which the solute leaves, by renal and extrarenal routes, the body fluids in question. If the solute is excreted entirely by the kidney and is measured in the urine, the net amount retained at a given time may be calculated. This value divided by the concentration in serum or plasma equals the volume of distribution at that time.

An example of this method of calculation of the volume of distribution is as



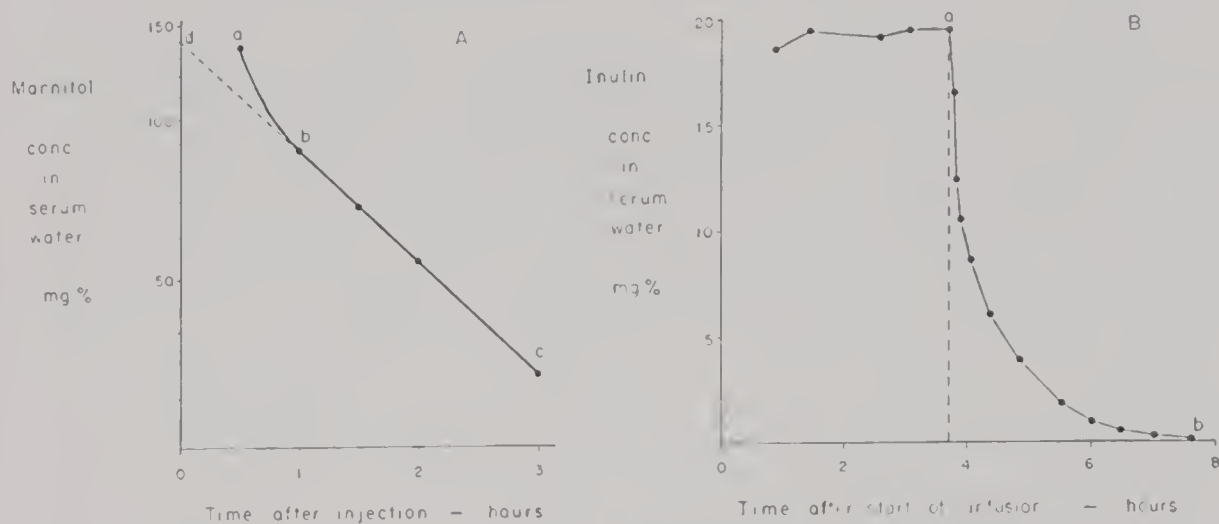


FIG. 3-3. THE DETERMINATION OF THE APPARENT VOLUME OF DISTRIBUTION BY (A) THE SINGLE INJECTION AND (B) THE CONSTANT INFUSION TECHNIQUES

In (A) the falling concentration of mannitol in serum water, after a single injection at zero time, is plotted semilogarithmically, *a b c*. The exponential slope, *b c*, indicates the rate at which mannitol leaves the extracellular fluid after mixing has been completed. The amount retained at any point along this part of the curve, divided by the concentration, yields the volume of distribution at that time; *b c* can be extrapolated back to zero time at *d* to determine the theoretical concentration if the mannitol injected were instantaneously distributed to equilibrium. (From the data of Elkinton (10b).)

In (B), after a constant infusion of inulin has brought the concentration in extracellular fluid to equilibrium, the infusion is stopped at *a* and all the inulin excreted until the concentration has fallen to zero at *b* is measured. This amount divided by the concentration at *a* yields the volume of distribution. (Modified from Gaudino, Schwartz and Levitt (10c).)

follows (for mannitol, fig. 3-3, A):

$$Q = 20.75 \text{ gm. in} - 11.46 \text{ gm. out} = 9.29 \text{ gm. retained}$$

$$C = 0.679 \text{ gm. per liter serum water}$$

$$V = \frac{9.29}{0.679} = 13.7 \text{ liters} \approx 22.1\% \text{ body wt.}$$

Thus, the volume of distribution of a solute such as mannitol, determined at points *a* or *b*, depends on an exact knowledge of the amount excreted since zero time. If the solute has been destroyed, metabolized, or excreted by other routes, the volume of distribution calculated by this method is erroneous. In such a case, however, it can be calculated if the rate at which the solute has left the body fluids by all routes is constant. This is done by extrapolating the straight line portion of the regression curve back to zero time (point *c*, fig. 3-3, A) and dividing the amount of solute injected by the concentration so defined. This is the concentration that would theoretically exist were the solute to be instantaneously distributed to equilibrium throughout the fluid compartment.

This type of calculation has been used for substances such as antipyrine which are known to be fairly rapidly metabolized in the body. Such a calculation is very sensitive to any error in determination of concentration. It has, however, the advantage of not requiring the collection and analysis of urine.

Rapidity of renal excretion, as in the case of the polysaccharides or other sugars such as inulin, sucrose, or mannitol, or rapidity of metabolism, as in the case of antipyrine, are undesirable characteristics of a solute used for this purpose. Slowness of diffusion of a solute, such as inulin, is also an undesirable characteristic, especially when there are large abnormal pools of fluid such as pleural effusion or ascites that must be penetrated. To use inulin under these circumstances in a manner that fulfills the prime requisite of diffusion to equilibrium, another method has been devised for the determination of the volume of distribution. This is the *constant infusion method*. It consists of maintaining a constant infusion until such time as equilibrium has been reached. At this point the infusion is stopped and the total amount excreted from that time on to the point of complete disappearance of the solute from the serum, is measured (fig. 3-3, B). This value represents the amount of solute retained in the fluid phase at the time of equilibrium; when divided by the concentration it yields the volume of distribution. Even with this refinement, the method is still subject to error due to changes in amount of the solute held in the renal dead space. This applies to any solute highly concentrated with respect to plasma as the solute passes through the renal tubule.

These methods of determining the apparent volume of distribution of an injected solute have been used for measuring various compartments of the body fluid, including the red cell and the plasma volume (8a-u), the extracellular fluid volume (9a-k, 10a-v), and the volume of total body water (11a-j). The various substances employed are shown diagrammatically in figure 3-4. The values obtained for the apparent volume of distribution of these substances are presented in tables 3-II and 3-III.

As shown in figure 3-4, many of the injected solutes extend beyond a particular fluid phase. This is to indicate that one of the chief difficulties in the use of this technic is the failure to fulfill the first requisite condition named above, i.e., that even diffusion of the solute occurs throughout the fluid phase with no transfer into another phase where it is present at a different concentration. For instance, in the measurement of *plasma volume* with T-1824, the Evans blue dye, it is well-known that the dye is attached to plasma proteins, and therefore goes where those proteins go. Since plasma proteins pass outside the plasma into the lymph and into interstitial fluid, the measurement of the plasma volume by this technic is somewhat larger than the true plasma volume. This is especially true in just those traumatic conditions in which there is an abnormal loss of plasma protein from the vascular system. The same difficulty is inherent in the tagging of plasma albumin with radioactive iodine,  $I^{131}$ . The estimation of

TABLE 3-II.

APPARENT VOLUMES OF DISTRIBUTION OR DILUTION AS A MEASURE OF BODY FLUID PHASES IN ADULTS						
PHASE	VOLUME					REFERENCES
PLASMA (ml./kg. body wgt.)						
Evans blue, T-1824	42	48	46	42		8c, e, f, p
I <sup>131</sup> Albumin	40					8t
"EXTRACELLULAR" PHASE (% body wgt.)						
Inulin	16	16	15	16		10c-e, p
Sucrose	20		21	18		10f, g, q
Mannitol	23	18	16	16		10b, h, i, p
Thiosulfate, S <sub>2</sub> O <sub>3</sub>		17				10j
Sulfate SO <sub>4</sub>	23					10f
Radiosulfate, S <sup>35</sup>	17					10k
Bromide	27	23	29			10d, g, l
Radiochloride, Cl <sup>36</sup>	27					10m
Radiochloride, Cl <sup>38</sup>	18	27				10n, g
Radiosodium, Na <sup>24</sup>	26	26	26	32	27	10o, n, d, g, s
Thiocyanate, SCN	22	27	25	22	24	10f, n, o, c, d
	27	23				10r, s
TOTAL BODY WATER (% body wgt.)						
Deuterium oxide, D <sub>2</sub> O	72	63	53	62	60	10n, 11e-h
Tritium oxide, THO	65	52				11i, j
Antipyrine	55	52	56			10e, 11f, j
Desiccation	68	59	66			11k-m

TABLE 3-III

BODY FLUID COMPOSITION IN INFANTS, AS MEASURED BY DILUTION TECHNIQUES					
Average values expressed as per cent of body weight					
PHASE	VOLUME		REFERENCES		
EXTRACELLULAR					
Thiocyanate, SCN	42		10s		
Radiosodium, Na <sup>24</sup>	44	43	10t		10s
TOTAL BODY WATER					
Deuterium oxide, D <sub>2</sub> O	75	77	10t		20a
Desiccation	69	75	11 1		20g



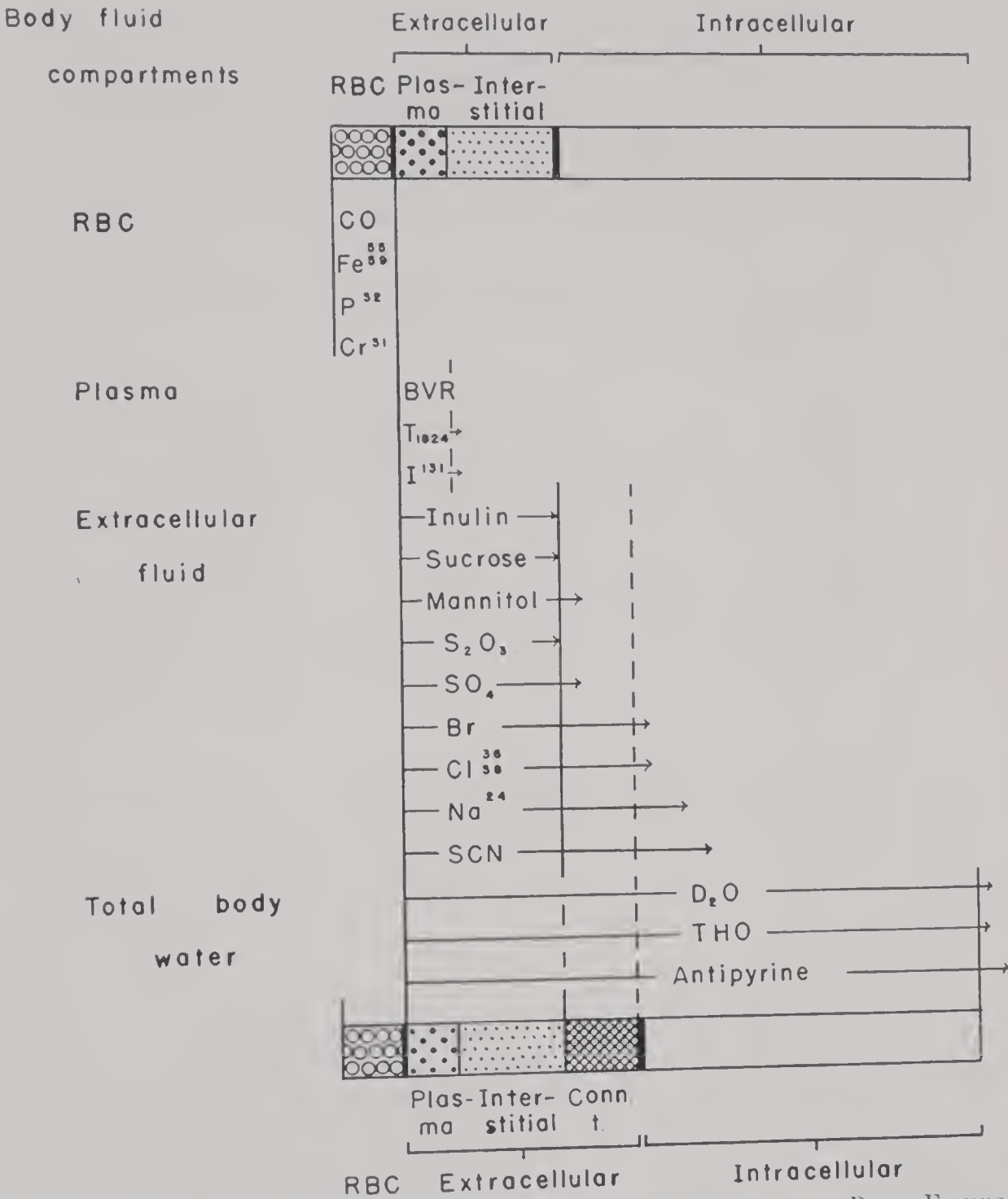


FIG. 3-4. SUBSTANCES USED TO MEASURE COMPARTMENTS OF THE BODY FLUIDS

It is obvious that many of the reference substances diffuse beyond the particular fluid phases, yielding volumes of distribution greater than the actual plasma, extracellular fluid or total body water.

the whole blood volume has one further difficulty. Since it is necessary to tag either the red cells or the plasma, the determination of the whole blood volume depends upon the relative cell volume of the blood as determined by the hematocrit. The hematocrit value for blood in a given organism may vary from one vessel to another or from large vessels to small vessels.

For this reason, it is always a question as to whether the hematocrit value used is representative of the vascular system as a whole. Despite these difficulties, however, these methods for measurement of plasma or red cell volume have been employed to investigate a wide variety of experimental and clinical conditions including dehydration, salt depletion, adrenocortical insufficiency, congestive heart failure, traumatic shock, hemorrhage, and burns.

In the measurement of the *extracellular fluid volume*, there are many difficulties. Thiocyanate and radioactive sodium have long been known to exceed the chloride space and to enter cells (9a). Moreover, chloride itself enters the cells of certain tissues (9b) and there is evidence that a moiety is present in muscle cells (9c) as called for by Conway's theory (9d). Therefore, the apparent volume of distribution of radioactive chloride must likewise exceed that of the true extracellular phase.<sup>1</sup> Since the apparent volume of distribution of inulin (and sucrose) is always the smallest of the solutes that readily cross the capillary barrier, it has been claimed to be a measure of the true extracellular phase, and on the basis of this claim large portions of sodium and chloride have been assigned to the intracellular fluid (9e-g). However, Cotlove (9h), Wallace and co-workers (9i) have recently presented evidence that suggests that our concept of the extracellular fluid has been oversimplified and that the inulin space is not the final answer to its measurement. These workers have demonstrated that chloride and sodium rapidly diffuse into collagenous connective tissue whereas inulin and thiosulphate do not. They suggest that the extracellular phase, outside of the plasma in the vascular system, should be partitioned into two subphases: the interstitial fluid which is an ultrafiltrate of plasma, and connective tissue. The inulin space defines only the plasma and the first of these two subphases while chloride and sodium diffuse rapidly through both subphases before entering more slowly the true intracellular fluid. Such a relationship received support from the observations of Singer *et al.* (9j) that sodium injected as sodium bicarbonate enters rapidly into about 22 per cent of the body weight, as compared to the average inulin space of 16 per cent, before diffusing more slowly into a further por-

<sup>1</sup> Wolf and McDowell (10v) have distinguished between the *apparent* and the *osmotic* volumes of distribution of sodium and chloride injected experimentally into nephrectomized animals; Conway and McCormack (10w) reached the same conclusion on theoretical considerations. The apparent and osmotic distribution volumes of sodium are the same and approximate the total body water; the osmotic volume of chloride is less, and is in accord with the theory that chloride is excluded from cells (which act like a perfect osmometer). This is evidence for: *a*) the free diffusibility of water between the extra- and intracellular phases of the body fluids, *b*) the status of sodium as a primary determinant of total osmolar concentration in the body fluids, and *c*) the predominantly extracellular position of chloride.

tion of the body. A similar interpretation can well be made of the findings of Swan *et al.* (9k) who showed that in nephrectomized dogs the volumes of distribution of sucrose, raffinose, and inulin were definitely smaller than those of mannitol, thiosulfate, and radiosulfate. This more complex concept of the extracellular fluid is shown diagrammatically at the bottom of figure 3-4 as an alternative to the simpler concept presented at the top of the figure. While the more complex hypothesis may explain many of the discrepancies observed, we are left at present with no method for the exact measurement of the "true" extracellular phase.

There are other difficulties with respect to this measurement in the intact organism. Not only do sodium and chloride, and perhaps some of the other solutes used for measurement, enter the intracellular fluid but they also cross cellular barriers into special fluid pools and depots. These have been termed by Moore (9l) the *transcellular fluids* and consist of fluids in the gastrointestinal tract, in serous and synovial cavities, in the lower urinary tract, and of cerebrospinal fluid, and of bile. Segregation of solutes in these depots may introduce definite errors in the measurement of the true extracellular fluid (9m). Bone has also been shown to exchange significant amounts of sodium with the extracellular fluids (9n) and so to introduce yet one more source of error. Nevertheless, the apparent volumes of distribution of these substances listed in table 3-II have been determined in many studies to approximate the magnitude of the extracellular compartment (10a-u), a fraction of the body which has been shown to be larger per unit weight in infants than in adults (10s, t) (table 3-III).

The absolute measurement of *total body water* has been attempted by observing the volume of distribution of numerous substances which are thought to diffuse through all the water of the body. Some of the substances suggested in the past have been urea (11a), thiourea (11b), and sulfanilamide (11c, d). Urea is difficult to use because of its rapid formation in the body. Thiourea is destroyed within the body and sulfanilamide enters cells in an unequal ratio to its extracellular concentration. More recently, water with labelled isotopes of hydrogen has been used for this purpose. These isotopes are *heavy water*, which is deuterium oxide or  $D_2O$  (10n, 11e-h), and *radioactive water*, which is tritium oxide or THO (11i, j). Studies indicate that possibly five per cent of heavy or radioactive water hydrogen exchanges in the body with hydrogen in substances other than water. Within the limits of this five per cent error, the apparent volume of distribution of these isotopically labelled waters should give a fairly good measurement of the total body water. Of the two, heavy water ( $D_2O$ ) is more easily obtainable but its analysis requires the use of complex apparatus for the fine determination of specific gravity or the use of a mass spectrometer. *Antipyrine* and its derivative, N-acetyl-4-amino-antipyrine, have



also been suggested for the measurement of total body water (10e, 11f, j). The chemical determination of this substance is less difficult but it has the disadvantage of being fairly rapidly destroyed in the body. It is therefore necessary to make an arbitrary correction for this decrement or to extrapolate the plasma disappearance curve back to zero time (fig. 3-3, A) in order to calculate its volume of distribution. The volumes of distribution of both labelled water and antipyrine are in reasonably good agreement with each other and with the values for total body water obtained by whole body desiccation (11k-m) or by specific gravity determination (12a, b). As in the case of the extracellular fluid, these methods indicate that in comparison to adults (table 3-II), the total body water of infants constitutes a greater relative proportion of the total body weight (table 3-III).

The specific gravity of the whole body is a function of its content of fat and water, and, where determined under research conditions, it can be used to calculate the proportion of each in a given subject. Such studies indicate a reciprocal relationship between water content and fat content of the body, i.e., the fatter the subject the less body water he has in relation to weight. For this reason, normal values for total body water are better related to the "lean body mass" which is made up of the tissues of the body minus the variable fat content. For the methods of calculation of the "lean body mass" see Section III of this chapter.

### *B. Isotope Dilution and Turnover*

The apparent volume of distribution technic has been extended to measure by dilution of radioactive isotopes the total body pool of certain solutes. This has been applied especially to the determination of total body sodium (10d, g, n, o, s, 13a-f) and total body potassium (13a, b, e, g, h). In the case of the latter, radioactive potassium,  $K^{42}$ , is injected and the net amount retained at the end of 24 hours is measured. Since only a small proportion of the body potassium is in extracellular fluid, the concentration in plasma cannot be used for the calculation. Instead, the total retention of the radioactive isotope is divided by the specific activity of isotope in the urine. That is, the ratio of the radioactive isotope to the ordinary isotope in the urine is assumed to be in the same ratio as in the whole body, and this ratio substitutes for the factor of concentration in the usual calculation of volume of distribution. Values so obtained for total body potassium have been of the order of magnitude of 45 milliequivalents per kilogram of body weight (see table 3-IV). This technic should provide a useful tool for the study of clinical disturbances, especially since Burrows *et al.* (13i) and Wilson *et al.* (13o) have found a close correlation between changes in the radioactive potassium pool and in balances of potassium. Exchangeable sodium and potassium may be measured simultaneously by isotope dilution (13n-q).

TABLE 3-IV.

TOTAL EXCHANGEABLE SODIUM AND POTASSIUM IN NORMAL ADULTS, AS MEASURED BY DILUTION OF THE RADIOACTIVE ISOTOPES									
Expressed in milliequivalents per kilogram of body weight									
INVESTIGATORS		MALES				FEMALES			
		Mean	Min.	Max.	N*	Mean	Min.	Max.	N*
SODIUM									
Forbes and Perley	13a	41.9	32.3	54.1	29	39.5	35.7	41.6	7
Deane and Smith	13e	37.9	33.9	50.7	6				
Edelman <u>et al.</u>	13b	41.4	31.6	46.0	11	41.0	31.4	45.9	3
Warner <u>et al.</u>	13c	40.6	37.6 <sup>#</sup>	43.6 <sup>#</sup>	13				
Miller and Wilson	13f	43.7	39.5	47.9	10	42.3	39.4	44.8	6
Ikkos <u>et al.</u>	9g	36.7	34.2	39.7	5	37.7	34.7	41.8	4
POTASSIUM									
Deane and Smith	13e	41.7	36.6	44.9	5				
Edelman <u>et al.</u>	13b,d	46.8	35.6	53.6	33	40.7	28.0	47.2	14
Aikawa <u>et al.</u>	13g					31.5	27.7	35.9	20
Blainey <u>et al.</u> <sup>‡</sup>	13h	45.8	27.4	84.2	17	35.0	21.3	61.8	7

\* N is the number of subjects  
# 2 standard deviations from the mean  
† hospital patients without diarrhea

There is another way in which radioactive isotopes are being used in the study of body fluid dynamics. Rate of *turnover* or exchange of solvent or solute between two compartments of body fluids can be determined when there has been no net transfer of either between them. Such uses of isotopically labelled water have been reviewed by Pinson (13j). Radioactive sodium has been employed by Gellhorn *et al.* (13k, l) in dogs and guinea pigs and Burch *et al.* (13m) in human subjects to demonstrate the rates at which sodium exchanges back and forth between plasma and interstitial fluid. The latter workers calculated that in the normal human subject approximately 32 per cent of the total plasma sodium and 13 per cent of the total interstitial sodium exchanged by diffusion each minute. Such a turnover is equivalent to approximately ten kilograms of salt per day. The distribution kinetics of intravenously injected radioactive potassium have been studied in detail by Ginsburg and Wilde (13r). This technic has been applied under experimental and pathological conditions to the study of solute exchange in various fluids of the body including transepillary exchanges, gastrointestinal fluid exchanges, plasma:red cell exchanges, as well as ex-

changes into cerebrospinal fluid, the aqueous humor of the eye, the placenta, the muscles, the nerves, and the liver.

### C. Balance Technic

This technic depends upon obtaining an accurate or quantitative knowledge of the intake and output of a body constituent. Much has been learned in this way about the function of many substances in the body other than the structural components of the body fluids. The balance technic as applied to the latter has been extremely useful, both scientifically and clinically, in increasing our knowledge of the physiology and in improving our therapy of body fluid abnormalities. Since much that we know has been obtained by this technic, and since it best demonstrates the quantitative results of fluid therapy in many conditions discussed in various sections of this book, the application of the balance method to the dissection of the fluid structure of the body is presented in detail. A system for quantitative interpretation of balance data, as applied to the study of body fluids, follows here. A more detailed critique of the balance method is to be found in the Appendix.

A balance is a measurement over a given period of time of the relation of intake of a substance to its output. When the output is less than the intake and some of the substance in question is retained in the body, the substance is in positive balance (fig. 3-5, days 5 to 13); when the output exceeds the intake, a negative balance obtains (fig. 3-5, days 14 to 17); when output just equals intake, the subject is in equilibrium (fig. 3-5, day 4). Such quantitative information concerning the principal solutes of the body fluids plus their concentration in plasma plus the body weight constitute *observed* data. From these observed data the *derived* data may be obtained by various systems of calculation. One such system is presented in detail with graphic illustrations in the following section. It should be emphasized that the values so derived estimate *changes* in fluid phases and solutes, in contradistinction to the absolute measurements made by the volume of distribution and isotope dilution technics described in the preceding section.

Since the total output of water cannot be readily measured due to losses by vaporization and sweat, the balance or change in total water must be calculated from changes in weight corrected for solids lost and food burned. Given such a calculated change in total water, it can be partitioned into extra- and intracellular portions in various ways. Usually this depends on the balance and change in concentration of a solute restricted mainly to extracellular fluid. Chloride is commonly employed in this capacity although all the questions are pertinent here in respect to its phase distribution which have been discussed above. Given such a solute, an absolute volume of extracellular fluid must be measured or assumed as a starting point for the calculation. Except in cases of



Patient : G.M. 42 ♀ W Rheumatoid arthritis

Therapy :

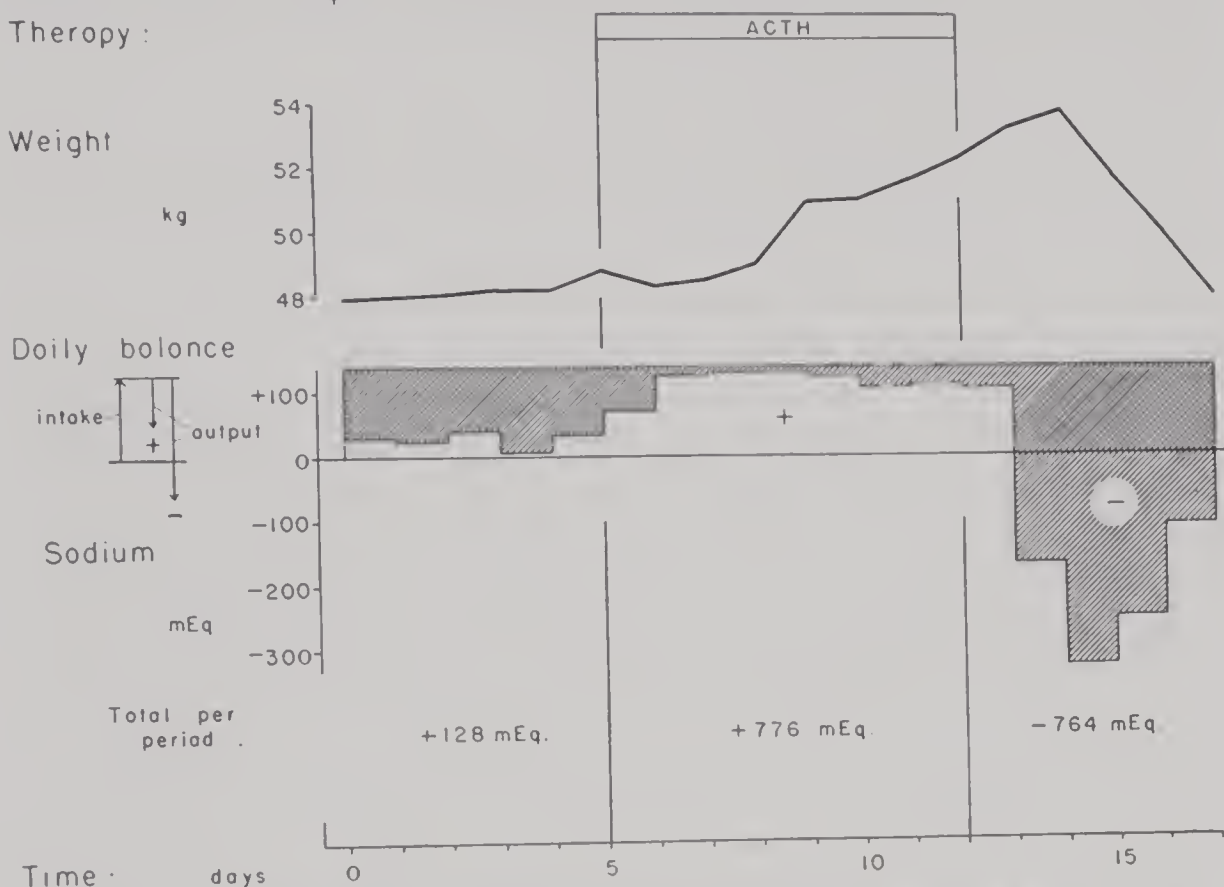


FIG. 3-5. CHANGES IN SODIUM BALANCE INDUCED BY THE ADMINISTRATION OF ADRENOCORTICOTROPHIC HORMONE (ACTH)

On a constant intake of sodium throughout the study, the output of sodium was diminished during the ACTH therapy and increased following its withdrawal. The result was a positive balance followed by a negative balance of the ion of approximately the same magnitude. The corresponding gain and loss of weight are shown. This is due to the concomitant retention and elimination of water. (From the data of Brown *et al.* (21b).

extreme edema or dehydration, as assumption of a volume is valid since such a value can vary over a considerable range without much effect on the calculated changes. The use of this technic in calculating changes in total body water, changes in extracellular fluid as equated with the chloride space, changes in intracellular fluid as the difference between the two, and changes in the distribution of certain electrolytes between these two phases, is shown in the following paragraphs and figures. These derived data are calculated according to formulae previously published (14a-c).

Change in *total water* ( $\Delta W$ ) is calculated from the change in body weight ( $\Delta Wt.$ ) corrected for the balance of solids and the metabolic mixture by the formula as derived by Peters, Kydd and Laviates (14d, l):

$$\Delta W = \Delta Wt. + (S_e - S_i) + (C + F + 0.54P) \quad (10)$$

where  $S_e$  and  $S_i$  = solids of excreta and ingesta, respectively,  
and  $C$ ,  $P$ , and  $F$  = carbohydrate, protein, fat metabolized, respectively.

The metabolic mixture is estimated as follows. Carbohydrate (C) burned is taken as the carbohydrate given. Protein (P) burned is taken as equivalent to the nitrogen excreted in the urine  $\times 6.25$ . The fat metabolized may be calculated from the insensible weight loss (IL) since the latter is related quantitatively to the total caloric value of the metabolic mixture and the carbohydrate and protein components are known. This relationship is formalized in the following equation (14e):

$$F = (IL - 2.12C - 1.69P)/3.78 \quad (11)$$

where IL is determined from the weights of the intake and the output and the change in total body weight ( $\Delta Wt.$ ) as follows:

$$IL = (wt. \text{ intake} - wt. \text{ output}) - \Delta Wt. \quad (12)$$

When IL is falsely large due to sweating, an average normal value must be assumed. Under such circumstances, however, balances of electrolytes are suspect.

Change in *extracellular fluid volume* ( $\Delta E$ ) is calculated from the change in concentration of chloride in extracellular water ( $[Cl]_E$ ), the balance of chloride ( $b_{Cl}$ ), and an initial extracellular volume ( $E_1$ ) either assumed or measured, in the following manner:

$$E_2 = (E_1[Cl]_{E_1} + b_{Cl})/[Cl]_{E_2} \quad (13)$$

$$\Delta E = E_2 - E_1 \quad (14)$$

$[Cl]_{E_1}$  and  $[Cl]_{E_2}$  are calculated from their corresponding concentrations in serum,  $[Cl]_{s_1}$  and  $[Cl]_{s_2}$  by use of a Donnan equilibrium factor of 0.95, as follows:

$$[Cl]_E = \frac{[Cl]_s}{0.95 \times [H_2O]_s} \quad (15)$$

where  $[H_2O]_s$ , the concentration of serum water in kilograms per liter is assumed, measured directly, or calculated from the serum total protein concentration ( $[P]_s$ ) in grams per cent, by the following equation (14f):

$$[H_2O]_s = 0.986 - 0.00745 [P]_s \quad (16)$$

Change in *plasma volume* ( $\Delta PV$ ) is calculated from the relative red cell volumes (hematocrit) ( $[Hkt]$ ) and hemoglobin concentrations ( $[Hb]$ ) of whole blood:

$$PV_2 = \frac{PV_1(1 - [Hkt]_2)[Hb]_1}{(1 - [Hkt]_1)[Hb]_2} \quad (17)$$

$$\Delta PV = PV_2 - PV_1 \quad (18)$$

where  $PV_1$  is measured or assumed (as 5.5 per cent of body wt. (14g)). This calculation is based on the assumption that the total circulating red cell mass

is unchanged and that the hematocrit value of the blood sample represents that of the blood of the whole body. The use of the hemoglobin concentration corrects for changes in the water content of red cells.

Change in *intracellular fluid* ( $\Delta I$ ) is calculated simply as the difference between the changes in total water and in extracellular fluid:

$$\Delta I = \Delta W - \Delta E \quad (19)$$

From the values for the volumes of extracellular fluid ( $E_1$  and  $E_2$ ), from the concentration of sodium and potassium in extracellular fluid ( $[Na]_E$  and  $[K]_E$ ), and from their external balances ( $b_{Na}$  and  $b_K$ ), the exchanges of these two ions between the extra- and intracellular phases of the total body fluids ( $\Delta Na_E$  and  $\Delta Na_I$ ,  $\Delta K_E$  and  $\Delta K_I$ ) are calculated as follows:

$$\Delta Na_E = E_2[Na]_{E_2} - E_1[Na]_{E_1} \quad (20)$$

$$\Delta Na_I = b_{Na} - \Delta Na_E \quad (21)$$

$$\Delta K_E = E_2[K]_{E_2} - E_1[K]_{E_1} \quad (22)$$

$$\Delta K_I = b_K - \Delta K_E \quad (23)$$

where  $[Na]_E$  is determined from the concentration of sodium in serum ( $[Na]_s$ ), the Donnan factor of 0.95 and the concentration of serum water ( $[H_2O]_s$ ) as follows:

$$[Na]_E = \frac{0.95[Na]_s}{[H_2O]_s} \quad (24)$$

Because of its small magnitude and the uncertainty of the proportion that may be un-ionized, the concentration of potassium in extracellular fluid ( $[K]_E$ ) is taken to be the same as that in serum ( $[K]_s$ ).

Change in intracellular potassium ( $\Delta K_I$ ) is further corrected by the nitrogen balance ( $b_N$ ) to indicate that portion of intracellular potassium that is transferred independently of the catabolism or anabolism of tissues, or "in excess of nitrogen," ( $\Delta K_I'$ ):

$$\Delta K_I' = \Delta K_I - \Delta K_p \quad (25)$$

$$\Delta K_p = 2.4 b_N \text{ or } 3.0 b_N \quad (26)$$

where  $b_N$  is expressed in grams and  $\Delta K_p$  in milliequivalents.

In cases where the concentration of nonprotein nitrogen in the body fluids has risen or fallen more than a few milligrams per cent during the balance period, the nitrogen balance must be corrected ( $b_N'$ ), using an assumed value for total body water ( $W$ ) as equal to  $\pm 0.65$  wt.:

$$b_N' = b_N - (\Delta NPN \times W) \quad (27)$$

The factor 2.4 in equation 26 has been taken to be the ratio of potassium in milliequivalents to nitrogen in grams in body tissue (muscle). However, the potassium:nitrogen ratio as measured by muscle analyses varies somewhat,



the range being 2.4 to 3.0. In the past, the authors have used a potassium : nitrogen ratio of 2.4 as above. Albright *et al.* recommend 2.7, while Darrow has used in his calculations a value of 3.0 (14h). Since Lilienthal and co-workers (2e) (see p. 70 above) have found a ratio of 3.5 milliequivalents of potassium to one gram of noncollagenous nitrogen, the higher ratios are probably more nearly correct.

In addition to the transfers of sodium and potassium, certain calculations can be made with respect to interphase exchanges of bicarbonate and hydrogen (14i-k). This method of approximation is likewise based on the chloride space and consists essentially of calculating hydrogen transfers from changes in the absolute amount of total extracellular bicarbonate corrected for hydrogen taken up or released by buffer proteins in blood and for hydrogen lost or conserved by the kidney. The resultant must approximate hydrogen moving in one direction or bicarbonate in the other direction, between extracellular and intracellular phases.

One further modification is essential in order to calculate the hydrogen exchanged with blood buffers: the total extracellular fluid must be subdivided into the two phases of plasma (p) and interstitial fluid (f). In addition, the red cells (r) are included with the extracellular phase (e). For each of these three "extracellular" subcompartments the change in absolute amount of bicarbonate ( $\Delta\text{HCO}_3^-$ ) is calculated from the initial and final volumes (v) and bicarbonate concentrations ( $[\text{HCO}_3^-]$ ):

$$\Delta\text{HCO}_3^- = V_2[\text{HCO}_3^-]_2 - V_1[\text{HCO}_3^-]_1 \quad (28)$$

Change in bicarbonate of plasma and red cells can be calculated as a unit, i.e., in whole blood, according to the above equation, from the bicarbonate concentration calculated from measured total carbon dioxide content and pH of whole blood, and from a measured or assumed blood volume of 80 milliliters per kilogram weight. Successive blood volumes ( $V_{b_2}$ ) are derived from the initial blood volume ( $V_{b_1}$ ) and the corresponding hemoglobin concentration ( $[\text{Hb}]$ ):

$$V_{b_2} = V_{b_1} \frac{[\text{Hb}]_1}{[\text{Hb}]_2} \quad (29)$$

Successive plasma volumes ( $V_p$ ) are calculated from the blood volumes ( $V_b$ ) according to the hematocrit and the interstitial volume ( $V_f$ ) taken as the difference between the total extracellular volume and ( $V_p$ ). The concentrations of bicarbonate in interstitial fluid ( $[\text{HCO}_3^-]_f$ ) are taken from those in plasma ( $[\text{HCO}_3^-]_p$ ) according to a Donnan factor of 1.16:

$$[\text{HCO}_3^-]_f = 1.16[\text{HCO}_3^-]_p \quad (30)$$

Having obtained the change in total bicarbonate of each subphase, that for the total extracellular fluid plus red cells ( $\Delta\text{HCO}_3^-_{e,r}$ ) is calculated:

$$\Delta\text{HCO}_3^-_{e,r} = \Delta\text{HCO}_3^-_r + \Delta\text{HCO}_3^-_p + \Delta\text{HCO}_3^-_f \quad (31)$$

The change in hydrogen is equivalent to that in the blood buffer anion (hemo-

globin and plasma protein) ( $\Delta\text{Buf}_b^-$ ), which is calculated according to the data of Dill *et al.* (14j, k):

$$\Delta\text{Buf}_b^- = [7.0 V_p + 2.3[\text{Hb}]_b V_b] \Delta\text{pH} \quad (32)$$

where  $[\text{Hb}]$  is the hemoglobin concentration in millimols per liter and  $\Delta\text{pH}$  is expressed in units of 1 = 0.01.

One further correction is necessary, namely, the balance of hydrogen ( $b_{\text{H}^+}$ ) calculated, in the absence of intake, from the urinary excretion of ammonia, ( $\text{UV}_{\text{NH}_4^+}$ ), titratable acid ( $\text{UV}_{\text{TA}}$ ) and bicarbonate ( $\text{UV}_{\text{HCO}_3^-}$ ):

$$b_{\text{H}^+} = -[(\text{UV}_{\text{NH}_4^+} + \text{UV}_{\text{TA}}) - \text{UV}_{\text{HCO}_3^-}] \quad (33)$$

The final calculation can then be made of the change in intracellular hydrogen ( $\Delta\text{H}_i^+$ ) that had to be transferred in or out of cells in association with these corrected shifts of extracellular bicarbonate:

$$\Delta\text{H}_i^+ = \Delta\text{HCO}_{3_e}^- + \Delta\text{Buf}_b^- + b_{\text{H}^+} \quad (34)$$

Since the transfer of hydrogen out of cells cannot be distinguished from the transfer of bicarbonate into cells, and vice versa, this relationship holds:

$$\Delta\text{H}_i^+ = -\Delta\text{HCO}_{3_i}^- \quad (35)$$

These exchanges of cations between phases are based on the assumption that chloride remains extracellular. Although this may not always be so, the probability is against there being enough of a shift of chloride across the phase boundary to invalidate the direction of the calculated transfers of cations. Where such an error does occur it will affect the calculated changes in intracellular sodium ( $\Delta\text{Na}_i$ ) to a far greater extent than those of potassium ( $\Delta\text{K}_i$ ) because of the predominantly extracellular position of the sodium ion. On the basis of statistical analyses, Schwartz and Wallace (15) have suggested that  $\Delta\text{Na}_i$  must be equivalent to approximately six per cent of the extracellular sodium before reliance can be placed on its value calculated in this manner. Due to the small proportion of body potassium in the extracellular fluid, values for  $\Delta\text{K}_i$  calculated from balances of lesser magnitude are generally more reliable. Highly derived values, such as those outlined above, must always be examined critically with respect to the basic assumptions underlying the calculations, the errors of measurement and analysis of intake and output, and the magnitude of the changes in the fluid constituents involved.

The system of calculating such derived data from observed balances, as presented above, can be shown graphically. Such presentation is advantageous in dissecting the fluid abnormalities in various clinical disturbances, and will be used extensively throughout this book. In the total organism, the body fluids can be described by a rectangle with volume as one co-ordinate and concentration as the other. The area, therefore, will be equivalent to the total amount of solute (fig. 3-6, A). This rectangle representing the total body fluid can then be divided into two principal phases, the extracellular and the intracellular. Between these phases and the external environment, certain solutes exchange

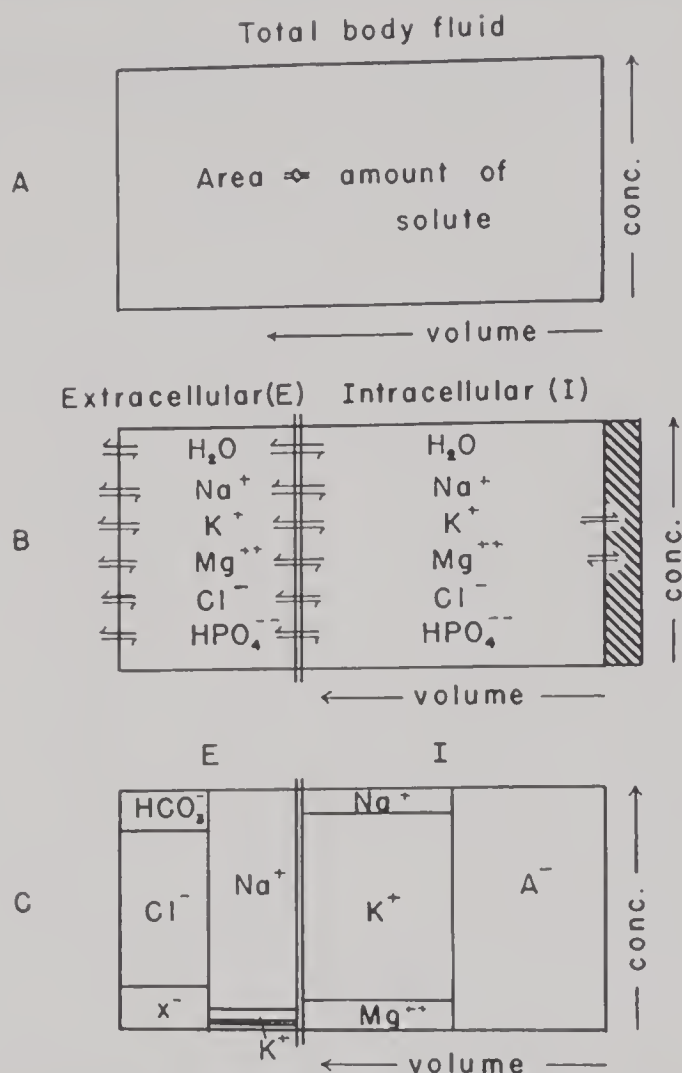


FIG. 3-6. GRAPHIC PRESENTATION OF THE BODY FLUIDS IN TERMS OF (A) TOTAL AMOUNT OF SOLUTE, (B) SOME OF THE PRINCIPAL FLUID CONSTITUENTS AND THEIR MOVEMENTS, AND (C) CATION:ANION PATTERNS SUPERIMPOSED ON THE SEVERAL PHASES OF BODY FLUIDS

and some of these exchanges can be quantitated or estimated by the balance technic detailed above. These solutes and their exchanges are illustrated in figure 3-6, B. It is to be noted that in addition a state of osmotic inactivity may occur within the cells (see below), which state is represented by the crosshatched area on the right. For purposes of illustration, one can take this rectangle divided into two phases and superimpose on each phase a bicolumnar pattern of cations and anions (fig. 3-6, C). Since the height of each ion represents concentration throughout the whole phase, the total amount of each ion is the height times the width of the phase, not the width of the individual cation or anion column. Given these schemata for representing the total body fluids and some of their main electrolytic constituents, these changes as calculated by the above equations are illustrated in figure 3-7.

Similar methods of calculating from balance data various alterations in the body fluids have been used by Darrow, by Albright and co-workers,



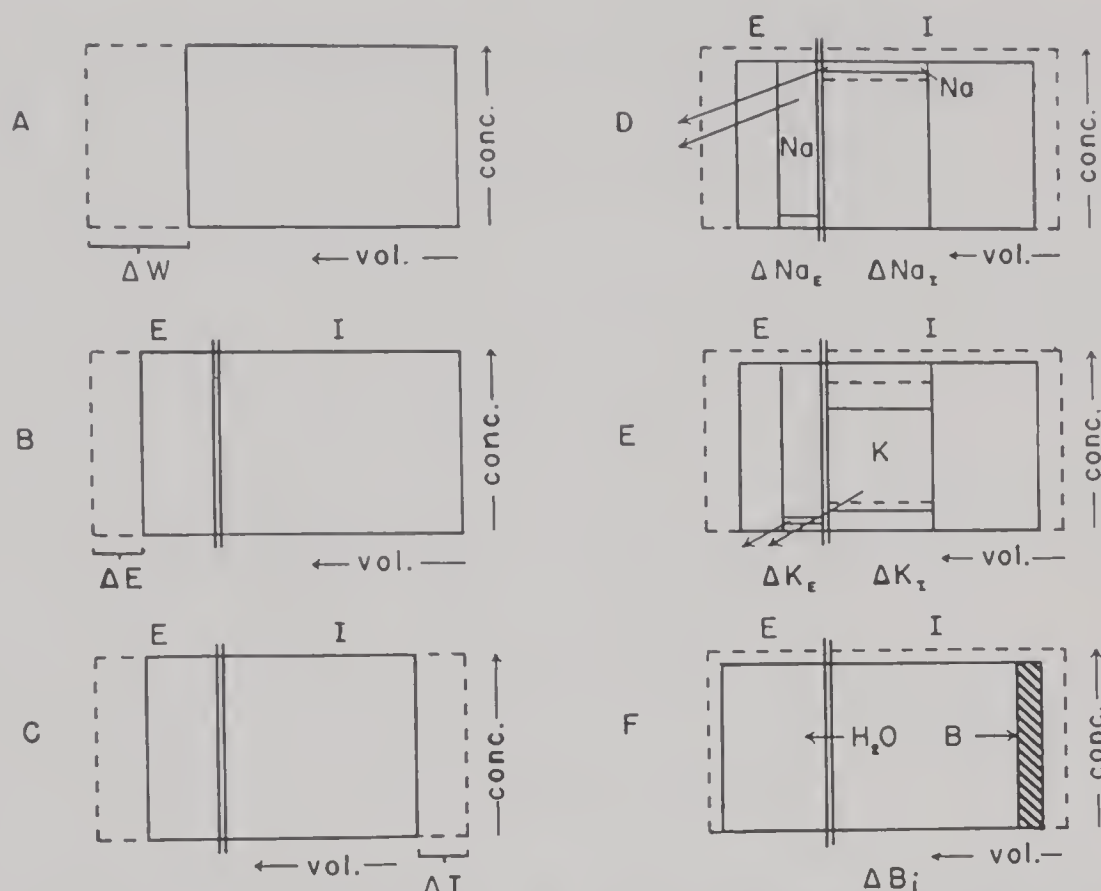


FIG. 3-7. SOME CHANGES IN BODY FLUIDS AS DETERMINED BY THE BALANCE TECHNIC

In rectangle A a loss of total body water and solids in the proportions in which they exist in the body is shown without subdivision into component parts. B illustrates a proportional deficit of extracellular water and electrolytes without change in concentration. Proportional deficits of extracellular and intracellular constituents are shown in C. In the next rectangle, deficits of extracellular and intracellular sodium out of proportion to the losses of water have lowered the concentrations of this electrolyte. Similar changes in potassium and water make up E. In the final figure, F, the osmotic activity of cell base has decreased during dehydration, releasing cell water to the extracellular spaces.

and by others (14h, 16a, b). The balance technic with values so derived has been employed in the investigation of a wide variety of experimental and clinical conditions. The former include dehydration, sodium and chloride depletion, potassium depletion, sodium excess, potassium excess, and metabolic or respiratory acidosis and alkalosis. Clinical conditions investigated by the balance technic include diabetic acidosis, pyloric obstruction, infant diarrhea, postoperative gastrointestinal fluid losses, acute and chronic renal insufficiency, renal tubular acidosis, nephrosis, cirrhosis, adrenocortical hypofunction and hyperfunction, diabetes insipidus, congestive heart failure, hypertension, and the endocrine and metabolic abnormalities associated with major surgical procedures (see tables 23-II to 23-VII, inc.).

The use of the balance technic in the study of some of these clinical conditions is illustrated in various portions of this book.

The estimation of changes in constituents of the body fluids from balance measurements has stemmed from the classic observations of Gamble, Ross, and Tisdall (17a) on the parallel movements of water, nitrogen, and the fixed bases in fasting epileptic children. These workers interpreted their findings to indicate that the bases of the body fluids were entirely dissociated or ionized and that on such an assumption the change in volume of water in the extra- and intracellular phases could be calculated from the balances of their respective cations, sodium and potassium. Equations for such calculations were formulated and this concept was critically reviewed by Peters and by Lavietes, D'Esopo, and Harrison (17b, c) who pointed out that balances of sodium and potassium would not indicate osmotic shifts of water due to changes in concentration of electrolytes in either phase. They did not, however, find any discrepancies between the balances of water and base in their experiments, presumably because the changes were not large enough to furnish definitive evidence. Water and base exchanges of greater magnitude, experimentally induced in dog and in man, were analyzed by the authors in collaboration with their late colleague, Dr. A. W. Winkler (17d). In about one-third of the periods discrepancies were found between the observed balance of sodium plus potassium and the balance of base predicted from the water balance and the change in base concentration in the body fluids (fig. 3-8). In the absence of alternative explanations of error in measurement, in analysis, or in assumptions underlying the calculations, such a discrepancy could best be accounted for by a change in the osmotic activity of the base within the body, presumably in the intracellular fluid.

Change in *osmotically active cell base* ( $\Delta B_i$ ) is calculated from the change in total water ( $\Delta W$ ) and from the concentration of sodium in extracellular fluid ( $[Na]_E$ ). Phase calculations derived from the chloride balance or from other measurements do not enter into this calculation. Assuming an initial volume of total body water ( $W_1$ ) and the concentration of osmotically active base in the body fluids ( $[B]$ ) to equal  $[Na]_E + 10$  milliequivalents per liter, the initial and final total amounts of osmotically active base in the body fluids ( $B_1$  and  $B_2$ ) are calculated from the formula:

$$B_1 = W_1[B]_1 \quad (36)$$

$$B_2 = (W_1 + \Delta W)[B]_2 \quad (37)$$

The predicted base balance ( $b_B$ ) is then derived from these values:

$$b_B = B_2 - B_1 \quad (38)$$

The difference between the predicted base balance and the observed balance of

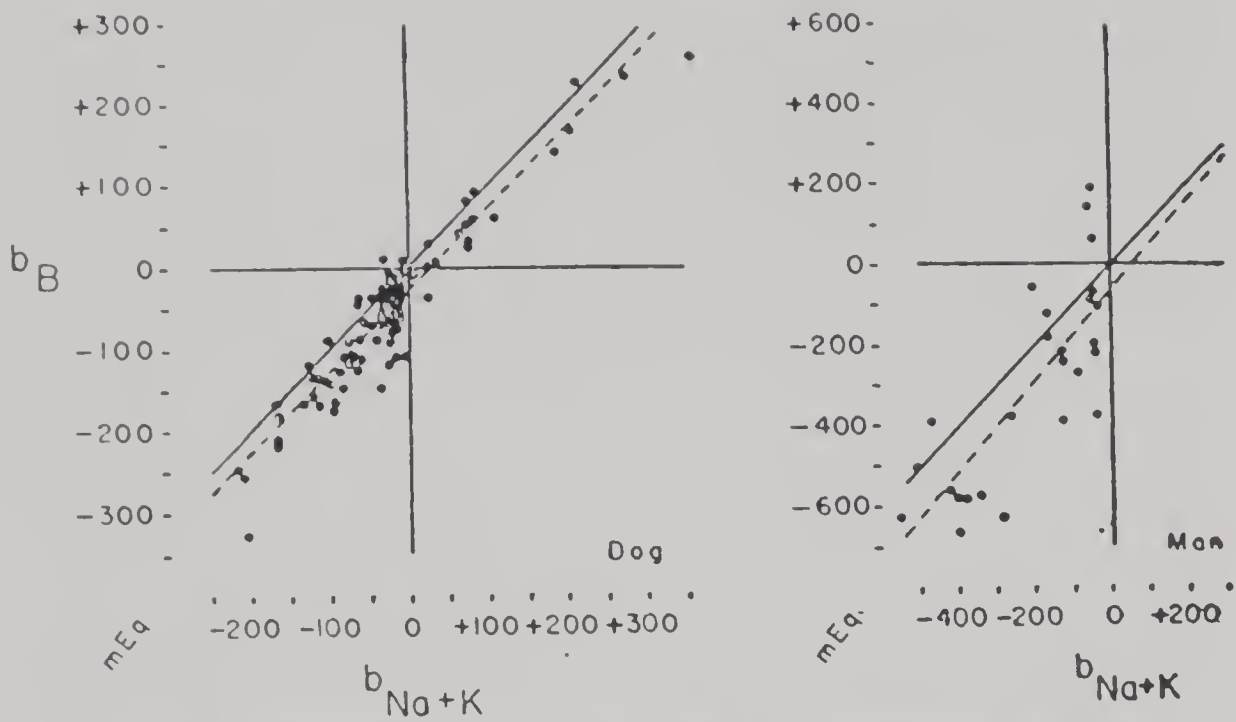


FIG. 3-8. EVIDENCE FOR THE OCCURRENCE OF CHANGES IN CELLULAR OSMOLARITY

This phenomenon was invoked to explain the discrepancies between the predicted ( $b_B$ ) and observed ( $b_{Na+K}$ ) base balances in dog and in man under various experimental conditions. (From Elkinton, Winkler and Danowski (17d).) The fact that the correlation between the measured and the theoretical balances of body base is not unity suggests that the osmotic activity of cell base has increased or decreased. Limitations of analytic technic have been considered in advancing this explanation. The segregation of base in non-ionic form probably involves chelation with other ions such as protein and phosphate.

sodium plus potassium ( $b_{Na+K}$ ) is therefore an internal change in osmotically active base ( $\Delta B_i$ ):

$$\Delta B_i = b_B - b_{Na+K} \tag{39}$$

Changes in osmotic activity of solutes in cell water are not, of course, restricted to cations. Anions are involved as well since electrical neutrality is preserved. Changes in the size and degree of dissociation of molecular aggregates, such as proteins and organic phosphates, within the cell are readily conceivable. But balances of these organic substances are less easily measured than are those of the inorganic cations. For this reason changes in osmotic activity of cellular solutes are more easily estimated in terms of cations or base.

Evidence for this phenomenon, as presented so far, has been of a negative nature, i.e., by exclusion of alternative explanations. Other more positive types of evidence are to be found in studies of isolated tissues. Yannet and Darrow (3c) and Mellors *et al.* (18a) observed that variations in intracellular fluid volume of skeletal muscle were 30 or 40 per cent less



than those predicted if osmotic equilibrium following changes in extracellular electrolyte concentration were achieved by transfers of water alone. Opie (18b) has found that the isotonicity of perfusion fluids of tissue slices from many different organs varies over a wide range. Robinson (18c, d) has reported large differences in the uptake of water by slices of the renal cortex of the rat under aerobic as compared to anaerobic conditions. Mudge (18e) has found that the presence of oxygen prevents the free exchangeability of some 40 per cent of radioactive potassium introduced into the rat kidney cortex slice, and Stanbury and Mudge (18f) localized non-exchangeable potassium in the mitochondria of the cells of the liver. It has been shown that the violent muscular activity of electric shock convulsions produces shift of water into cells, indicating a transient increase in the total effective osmolar concentration (18g). Similar water shifts following the administration of acids and metabolic poisons, and the production of anoxia, have been observed by Hamburger and Mathé (18h). Other evidence has been adduced from exchanges in a variety of clinical conditions (4c, 14b, c, 18i). Because of the magnitude of some of these changes, cellular osmolarity must be considered as a factor in any clinical disturbance of fluid balance. Its relevancy to the other forces of fluid exchange is shown in figure 1-9. Robinson and McCance (18j) have reviewed this evidence in detail and have postulated an active transport of water.

The validity of the balance technic in estimating alterations of the body fluids thus rests on a wide spectrum of experimental methods. Data derived from balances have correlated well with data obtained from tissue analyses, from volumes of distribution, and from isotope dilution studies. As research technics in this field are extended, more refinements may be expected in the application and interpretation of balance measurements. But already the balance technic has proved a major tool in the elucidation of the normal and pathological physiology of the body fluids.

#### *D. Regional Exchanges of Fluid*

So far the body fluids of the intact organism have been considered as a single polyphasic homogeneous system. As indicated in chapter 1 and in figure 1-11, this is an oversimplified concept which fails to take into account the multiplicity of widely separated tissues containing these fluid phases and which are connected only by the circulation. It is reasonable, therefore, to consider the various methods available for the study of exchanges and alterations in the distribution of water and electrolytes in various regions of the body.

It has long been recognized that variations in *blood flow* to different parts of the body occur under a wide variety of conditions. Methods of measure-

ment of regional blood flow have included the plethysmograph (which measures changes in volume of a limb or organ) and a large number of clearance technics. Some of these will be mentioned here, but will not be discussed in detail. Cerebral blood flow has been measured by the clearance of nitrous oxide (19a), hepatic blood flow by the clearance of bromsulphthalein (19b), renal blood flow by the clearance of paraminohippurate (19c). Flow of blood through the heart, or cardiac output, strictly speaking, is also a regional blood flow and is likewise quantitated by many variations of the clearance technic (19d), i.e., by the Fick principle, the basic equation for which is

$$\text{Flow} = \frac{\text{amount of solute cleared}}{\text{change in concentration}} \quad (40)$$

As these methods are being applied to many experimental and clinical conditions much is being learned of interrelationships of the intravascular fluid dynamics of different parts of the body.

Transfers of water and solutes in the various organs of exchange with the external environment, the skin, the lungs, the gastrointestinal tract, and the kidneys, are regional exchanges of fluid. These exchanges have already been discussed in chapter 1 and the methods of their elucidation will not be elaborated upon.

The several specialized "transeellular" fluids, alluded to previously (p. 80), have lent themselves especially to study by technics of isotope turnover (p. 81). This is well illustrated by the recent demonstration (19e) of the rapid and simultaneous exchange of heavy water,  $D_2O$ , between blood and the cerebrospinal fluid throughout the entire cerebrospinal system. This evidence casts doubt upon the previously held concept that this fluid is formed entirely in the choroid plexus of the third ventricle.

Other methods of determining regional fluid abnormalities are being developed. Kety (19f) used the uptake of radioactive sodium to measure the removal of fluid from subcutaneous tissues, and this technic has been studied by others (19g-j). Direct biopsies of tissues have been taken from certain sites in the body for analysis of water and electrolytes (2e, 3d, 5a-f). Since some clinical disturbances of fluid balance consist predominantly of regional abnormalities of fluid distribution within the body further development of methods for their study is a highly promising field for future investigation.

### III. Correlated Chemical Dissection of the Body

Chemical analysis of the body after death for its content of solids, fat, and fluids, as done in dogs by Harrison, Darrow, and Yannet (1a) (fig. 1-3) and in humans by Widdowson, McCance, and Spray (1b), has now been extended to the chemical dissection of the living body by means of the

various methods outlined in this chapter. Fluid compartments can be approximated from the volume of distribution of various test solutes and the total "pools" of electrolytes between extra- and intracellular phases depend on the accurate measurement of the extracellular fluid volume (table 3-II). Since this measurement has yet to be validated, data so derived are at best rough approximations. Further inaccuracies are introduced by the unpredictable extent of transfer into transcellular fluids and bone. With these reservations, however, absolute values for these components of the body can be calculated and tabulated as has been done by Moore and his co-workers (20a) in their excellent presentation of this subject (table 3-V and figure 3-9).

The amount of fat in the body can be calculated from the total body specific gravity or from the total water content as determined by a volume of distribution technic. The former method has been worked out by Behnke (12a, b, 20b) and the resulting data agree well with those obtained by the second method. Pace (20c), using isotopically labelled water to measure the water content of the body, calculated the per cent fat by the following equation which is based on the assumption that the water content of lean (non-fatty) tissue is 73 per cent:

$$\% \text{ Fat} = \frac{100 - \% \text{ H}_2\text{O}}{0.732} \quad (41)$$

McCance and Widdowson (20d) have made a similar calculation, based on the less satisfactory measurements of extracellular fluid and total body water by the volumes of distribution of thiocyanate ( $E_{\text{SCN}}$ ) and ingested urea ( $W_{\text{urea}}$ ), respectively.

The fat ( $F$ ) in the body was calculated as the total body weight ( $Wt.$ ) minus the sum of the weights of the extracellular fluid ( $E_{\text{SCN}}$ ), the cell mass ( $CM$ ), and the minerals ( $m$ ):

$$F = Wt. - (E_{\text{SCN}} + CM + m) \quad (42)$$

where:

$$CM = (W_{\text{urea}} - E_{\text{SCN}})/0.67 \quad (43)$$

since 67 per cent of the cell mass is cell water (the difference between  $W_{\text{urea}}$  and  $E_{\text{SCN}}$ ), and where

$$m = 0.075 (CM + E_{\text{SCN}}) \quad (44)$$

Using this method of calculation, these authors have studied the relationships of fat, extracellular fluid, and cell mass in a series of normal, obese, and undernourished subjects.

Obviously, the fat, the water, and the solid content of the body can vary



TABLE 3-V.

TOTAL BODY COMPOSITION IN THE ‘‘AVERAGE’’ ADULT*				
	MALE		FEMALE	
Weight, kgm.	70		57	
Surface area, sq.m.	1.73		1.60	
Specific gravity	1.067		1.039	
Total body water (D <sub>2</sub> O), liters	43.0		29.0	
ml. per kgm. wt.		614		509
Total body fat, kgm.	11.0		17.0	
gm. per kgm. wt.		157		298
Total body fat-free solids, kgm.	16.0		11.0	
gm. per kgm. wt.		229		193
Lean body mass, kgm.	59.0		40.0	
gm. per kgm. wt.		843		702
Total body nitrogen, kgm.	1.9		1.3	
gm. per kgm. wt.				
Total exchangeable sodium, mEq.	2950		2250	
mEq. per kgm. wt.		42.2		39.5
Total exchangeable potassium, mEq.	3200		2300	
mEq. per kgm. wt.		45.7		40.3
Extracellular water				
Sodium (3 hour), liters	18.0		13.0	
ml. per kgm. wt.		257		228
Inulin, liters	11.0		8.5	
ml. per kgm. wt.		157		149
Thiosulfate, liters	11.5		9.0	
ml. per kgm. wt.		164		158
Intracellular water, liters	31.5		20.0	
(based on Thiosulfate)				
ml. per kgm. wt.		450		351

\*Modified from Edelman *et al.* (20a)

independently of each other, and this fact must be kept in mind when interpreting data obtained by the methods outlined in this chapter. For this reason, the concept of the lean body mass has been promulgated to avoid the shifting reference point of a total body weight which includes fat. In figure 3-10 are illustrated some of the various combinations of fat, lean body mass, and total body weight that may exist irrespective of any abnormality in body fluids *per se*. Equations for calculating changes in the lean body mass ( $\Delta\text{LBM}$ ) from the nitrogen balance ( $b_N$ ) have been formu-

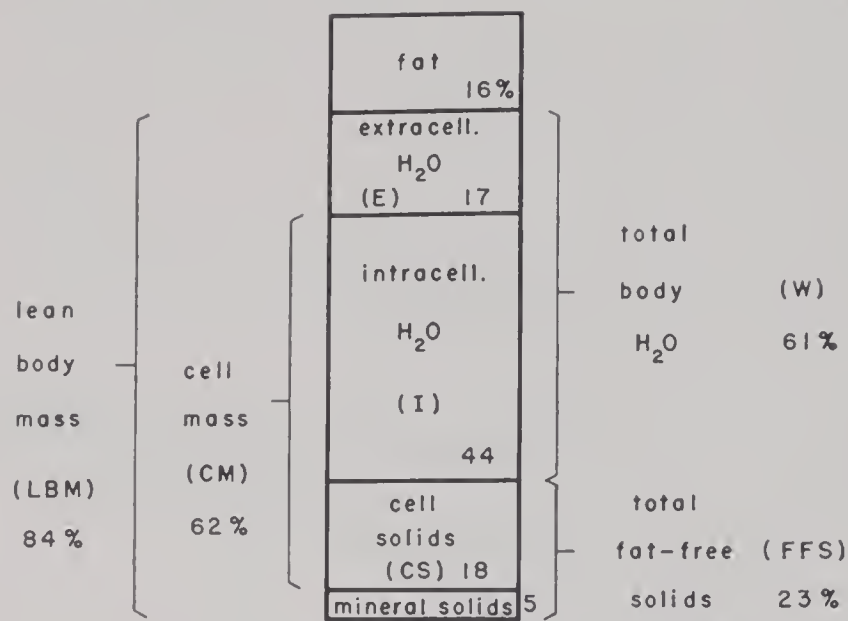


FIG. 3-9. TOTAL BODY COMPOSITION OF THE AVERAGE ADULT MALE  
Values taken from Edelman *et al.* (20a) in table 3-V

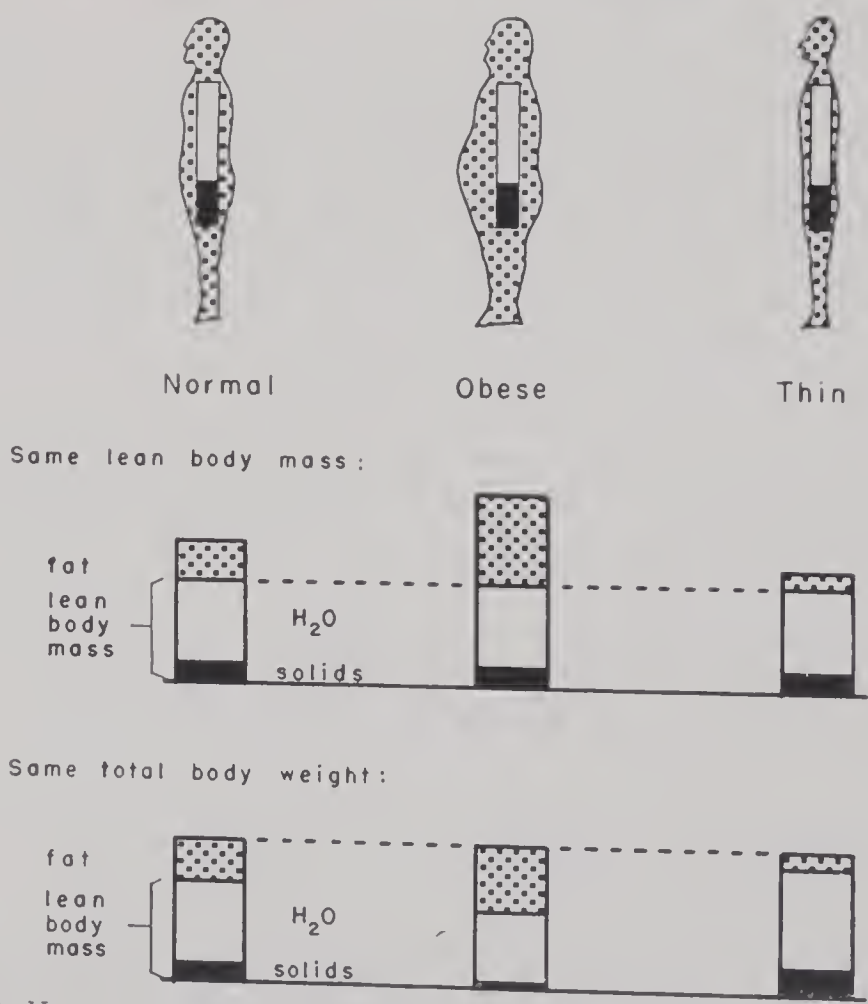


FIG. 3-10. VARIOUS RELATIONSHIPS OF FAT, WATER, AND SOLIDS ACCORDING TO BODY HABITUS

It is obvious that the amount of fat affects body weight and alters the *percentage* of body weight attributable to water. The *absolute* amount of water can be the same in normal, obese, and thin individuals whose fundamental body structure is the same.

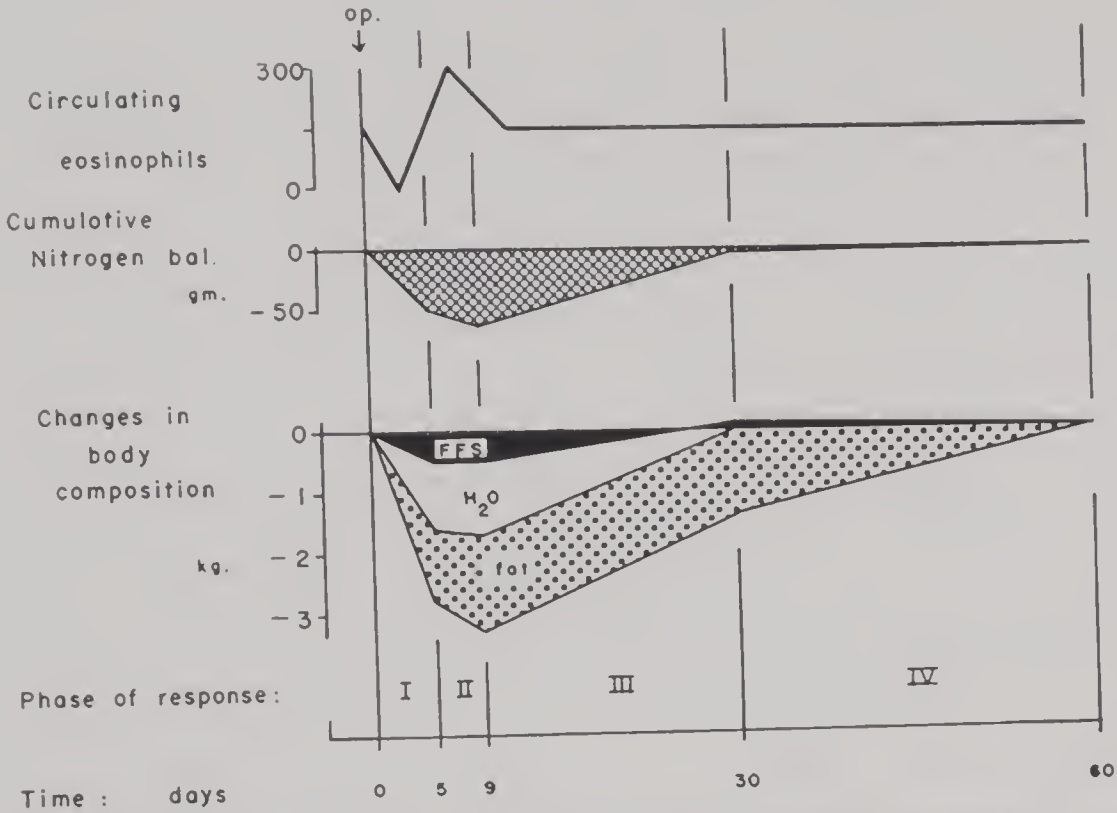


FIG. 3-11. CHANGES IN BODY COMPOSITION IN DISEASE: RESPONSE OF THE NORMAL PERSON TO THE TRAUMA OF OPERATION

(From Moore (20f).) Following operation body mass is lost including protein, fat, water, and fat-free solids. Included in the last of these is potassium.

lated by Moore and co-workers (20a):

$$\Delta \text{LBM} = b_N \times 30 \tag{45}$$

and on the assumption that 73 per cent of the lean body mass is water, the change in lean body water and lean body solids can readily be calculated. Such a calculation, of course, is not valid where abnormal loads of water exist in sick patients.

The absolute lean body mass in kilograms may also be calculated from the excretion rate of creatinine or the consumption of oxygen according to the formulae of Miller and Blyth (20e):

$$\text{LBM} = 20.97 + 0.5161 \text{ UV}_{\text{creatinine}} \tag{46}$$

where  $\text{UV}_{\text{creatinine}}$  is the excretion rate in milligrams per hour.

$$\text{LBM} = -7.36 + 0.2929 (\text{O}_2 \text{ consumption}) \tag{47}$$

where the basal  $\text{O}_2$  consumption is measured in milliliters per minute.

Clearly, much can be learned of *changes* in the amounts and distribution of the structural constituents of the body fluids by the measurement of metabolic balances, as detailed in this chapter. The correlation of such

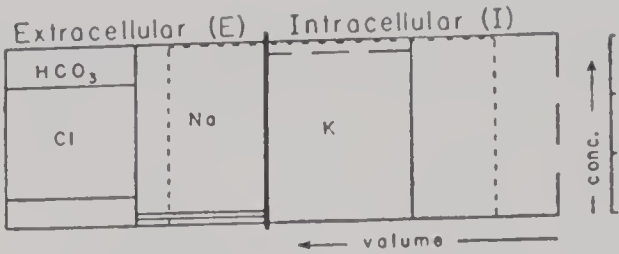


Cardiac Edema

Mercurial diuresis (L.D.)

Before

Serum conc  
meq per l.  $\text{HCO}_3 = 34$ ,  $\text{Na} = 144$   
 $\text{Cl} = 95$ ,  $\text{K} = 4.2$



Therapy for 7 days

	Dialysed milk (Na-free) and H <sub>2</sub> O.	Digitoxin p.o.,	Mercurhydrin i.m.
<u>Exchanges</u>	<u>H<sub>2</sub>O</u>	<u>Cl</u>	<u>Na</u> <u>K</u>
Given	14.5 liters	275 meq.	11 meq.                      556 meq.
Excreted	13.1 "	1045 "	1259 "                      175 "
Retained-E	- 8.0 "	- 770 "	- 1220 "                      - 31 "
Retained-I	- 5.1 "		- 28 "                      411 "
- I (in excess N)			368 "

After

$\text{HCO}_3 = 31$ ,  $\text{Na} = 139$   
 $\text{Cl} = 101$ ,  $\text{K} = 4.4$

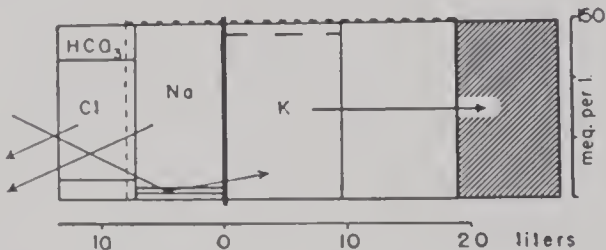


FIG. 3-12. CORRELATED CHEMICAL DISSECTION OF CONGESTIVE HEART FAILURE: ANALYSIS OF BODY FLUID ABNORMALITIES BY BALANCE STUDY DURING DIURESIS

The data are summarized and the estimated changes plotted on a volume-concentration diagram (as in fig. 3-6, c). The salient features of cardiac edema are demonstrated to be retention of intracellular as well as extracellular water, extracellular sodium excess, cellular potassium deficit, and increased cellular osmolarity. (From Squires, Crosley and Elkinton (14c).)

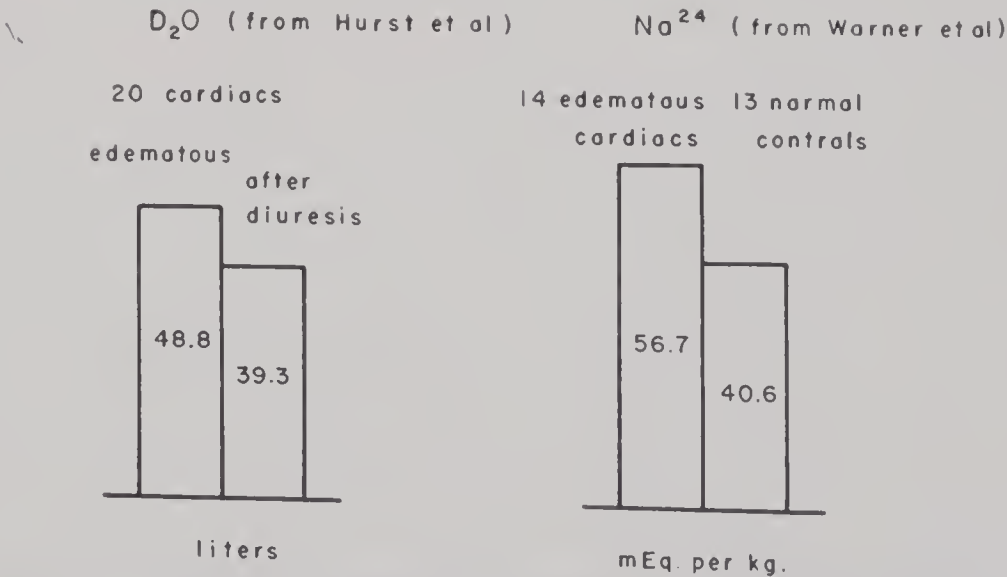


FIG. 3-13. CORRELATED CHEMICAL DISSECTION OF CONGESTIVE HEART FAILURE: ANALYSIS OF BODY FLUID ABNORMALITIES BY ISOTOPE DILUTION

The dilution studies indicate excess of total water and total body sodium. (From Hurst *et al.* (21c) and Warner *et al.* (13c).)

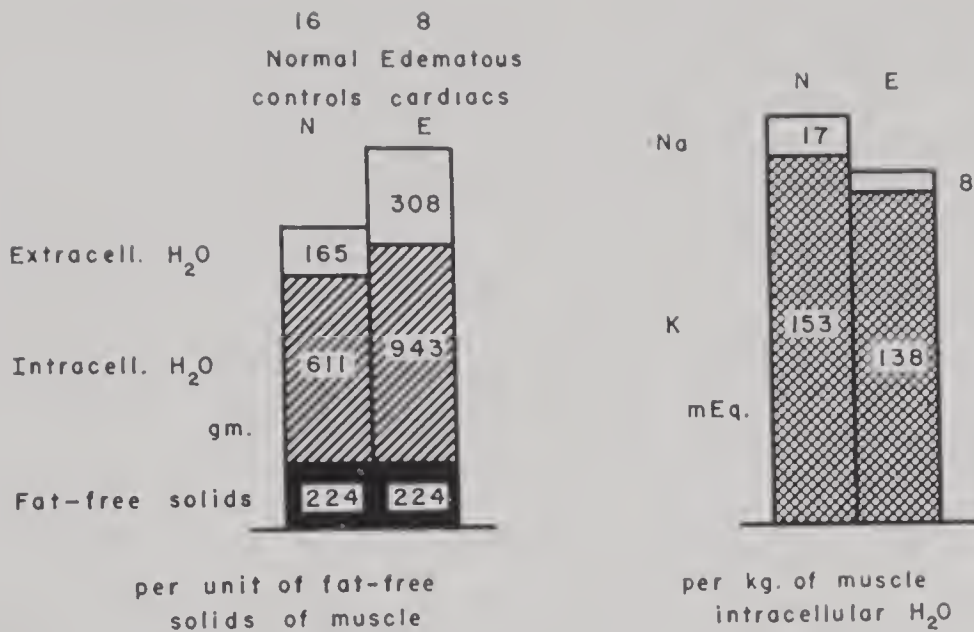


FIG. 3-14. CORRELATED CHEMICAL DISSECTION OF CONGESTIVE HEART FAILURE: MUSCLE ANALYSIS

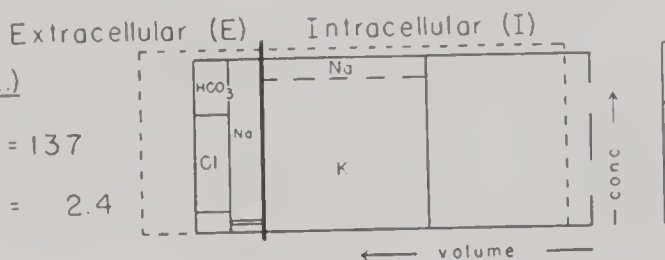
The muscle analysis shows an increase in intracellular as well as extracellular water and a lowered cellular content of Na and K in relation to water. (From Talso *et al.* (5f).)

Potassium Deficiency and

Alkalosis in Starvation (W.L.)

Before

Serum conc. meq per l.  
 $\text{HCO}_3 = 45$ ,  $\text{Na} = 137$   
 $\text{Cl} = 79$ ,  $\text{K} = 2.4$



Therapy for 10 days:

Milk and H <sub>2</sub> O p.o. 10 days,		$\text{K}_2\text{HPO}_4 + \text{KH}_2\text{PO}_4 + \text{KCl} + \text{NaCl}$ iv 4 days			
Exchanges	H <sub>2</sub> O	Cl	Na	K	
Given	41.9 liters	1167 meg.	855 meg	1115	meg.
Excreted	40.6 "	487 "	901 "	231	"
Retained - E	4.4 "	680 "	660 "	46	"
Retained - I	-3 l "		- 706 "	838	"
- I (in excess of N)				778	"

After

$\text{HCO}_3 = 28$ ,  $\text{Na} = 143$   
 $\text{Cl} = 104$ ,  $\text{K} = 5.7$

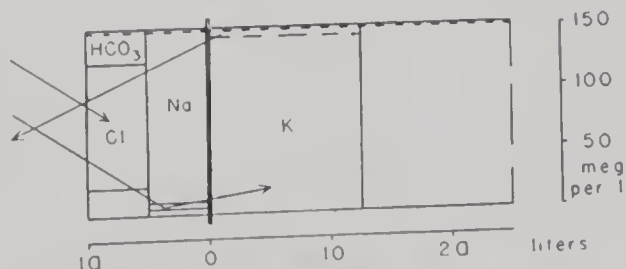


FIG. 3-15. CORRELATED CHEMICAL DISSECTION OF POTASSIUM DEFICIENCY WITH METABOLIC ALKALOSIS: ANALYSIS OF ABNORMALITIES BY BALANCE STUDY DURING RECOVERY

The data show that the abnormal state was characterized by intracellular deficit of potassium and excess of sodium (see also fig. 11-9). (From Elkinton, Squires and Crosley (21c).)

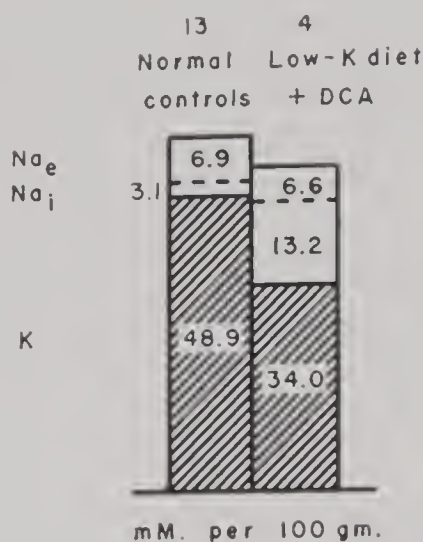


FIG. 3-16. CORRELATED CHEMICAL DISSECTION OF POTASSIUM DEFICIENCY WITH METABOLIC ALKALOSIS: MUSCLE ANALYSES FROM EXPERIMENTAL STUDIES IN RATS

The muscle from animals treated with a low-K diet and desoxycorticosterone contained less potassium and more intracellular sodium than the normal contents. (From Darrow *et al.* (4n).)

balance data with absolute measurements by volume of distribution and isotope dilution technics, and the interpretation of such data in the light of underlying assumptions and the concept of lean body mass, have truly made possible the chemical dissection of the living body. Much remains to be done to improve these tools of investigation and to apply them to the elucidation of the pathological physiology of myriad states of disease. Examples of applications of these methods are illustrated in figures 3-11 through 3-16.

**SUMMARY:** Information concerning the status of body fluids has been accumulated by direct analyses of tissue samples or of entire carcasses using chloride as an index of the extracellular phase, by *in vitro* studies of surviving tissues, by determination of the apparent volume of distribution or dilution of radioactive and non-radioactive test substances, by determination of the whole body specific gravity in conjunction with the lean body mass as reflected in creatinine excretion, by measurement of rates of isotope turnover, and finally by the balance technic. Information derived by means of these procedures enables us to define or estimate the composition of the body fluids in health and draw conclusions concerning modifications which result from disease.

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## PART II

### *Basic Principles as Common Denominators in Clinical Situations*





“Water . . . is the image of the ungraspable phantom of life; and this is the key to it all.”

Herman Melville in *Moby Dick*

## *Chapter 4*

# THE WATER AND THE ELECTROLYTES OF THE BODY IN HEALTH

### I. Water

In the preceding chapters a dynamic concept of the origin, distribution, function and regulation of the body fluids has been formulated. In this chapter and the next seven which follow, these facts will be used to provide insight into regulatory mechanisms in health and the disturbances which result from disease.

#### *A. Total Body Water*

The water of the body is in the main derived from water present as such in the food and fluids of the daily intake. In addition a small amount, some 200 to 300 cc. per day, is formed during the combustion of carbohydrate, fat and protein inside of cells (1a-d). It has already been pointed out that in health the body water makes up some 45 to 75 per cent of the body mass. This range of values has been obtained by one or another of a group of technics. Thus desiccation of animal and of human tissues, the volume of distribution of index substances such as thiourea, antipyrine, or heavy water, and the specific gravity of the body as a whole have all been used, but this list by no means exhausts the procedures employed for this purpose (2a-i). Unfortunately at the present time all of them are too cumbersome for routine clinical use but under selected circumstances they permit estimates of the probable volume of water in the body.

At first sight this extensive range of normal for the percentage of body water would suggest that this component of the body can vary markedly even in health. Recollection of the fact that our day to day body weight remains quite constant, so clearly illustrated in figure 1-14, should effectively and promptly dispose of this possibility. Actually the range of normal

for total body water as given above encompasses the lower and upper limits of values in a group of healthy people. In any particular healthy, non-growing subject, however, the percentage of body water varies but little. This holds true even in the face of wide fluctuations in the intake of fluids. The different percentages of body water in different individuals are largely and perhaps entirely related to the amounts of fat present in each of their bodies (2j-l). A graphic presentation of this fact makes up figure 3-10. This view is quite acceptable since the relative immiscibility of water and of lipids is well recognized. Actually, in terms of *total volume of water* the fat and the lean individual have the same amount provided their bodies are comparable in size in every other respect save the amount of lipid.

### *B. Extracellular and Cellular Water: Concentrations and Volumes*

It will be recalled that the chief body compartments consist of: a) the plasma, b) the interstitial spaces which in combination with plasma are referred to as the extracellular fluid, and c) the fluid within the cells. This was illustrated in figures 1-1, 1-11 and 3-9. One milliliter of serum or plasma contains in health between 0.925 and 0.940 gram of water. Interstitial fluid is approximately 99 per cent water while in cells, taking the erythrocyte as an example, the percentage of water ranges from 67 to 80 (3a-c).

As in the case of the total water of the body, the volumes of the various body fluid compartments or subdivisions have been estimated by a variety of means. In the case of plasma the volume has been approximated by tagging the subject's own plasma proteins with a known amount of dye, by adding a small though known amount of radioactively labelled protein to the patient's own plasma stores, by using carbon monoxide to measure the total volume of red blood cells in the circulation or by administering a known volume of cells tagged with radioactive phosphorus or iron (4a-i). In general these studies indicate that the plasma volume is equal to some five per cent of the body weight in health. Changes in the volume of plasma can be approximated by serial measurements of the hematocrit and hemoglobin (4j, k).

It has been pointed out that attempts to measure the volume of the extracellular fluid as a whole, i.e., the volume of the plasma and of the interstitial fluid have involved the use of a wide variety of test substances. In each new trial it was hoped that when an accurately measured amount of the material was administered it would promptly and uniformly distribute itself in the water of plasma and the interstitial spaces without attachment to tissues or other solutes, without penetration into cells, and without destruction of or addition to the carefully measured aliquot of the test substance. In all these studies it has been felt, though in all probability with limited justification, that excretion via the kidneys could be measured and the amount subtracted from the initial dose. With the passage of time it



has become clear that substances such as thiocyanate, sulfonamides, radioactive chloride and radioactive sodium give excessively high values for extracellular volume, i.e., 25 to 30 per cent of the body weight, and that the lowest values, about 15 per cent of the body weight, are obtained when the volume of distribution of inulin or sucrose is used as the index. In between these two extremes fall the results obtainable with sugars such as sucrose and mannitol, with bromide, and with sulfate or thiosulfate (5a-k). In some laboratories the balance of and the changes in the serum levels of chloride are used as an index of increases or decreases in extracellular fluid (5l). This method does not however measure the total amount of extracellular water. The role of connective tissue as a participant in the extracellular distribution of chloride has already been discussed in chapter 3.

In brief therefore it can be stated that at this time no general agreement is present as to what proportion of the true extracellular volume is being measured by any one of these procedures. There is a general concession however that none of them falls into the category of a simple and readily available index of extracellular volume, even when one is willing to accept whatever errors may be inherent in the technic. For clinical purposes we agree, as a working hypothesis or approximation, that in health the extracellular fluid makes up some 15 to 20 per cent of the body weight of the average nonobese adult. In the infant this value will be about five per cent greater (5m). It naturally follows that if body water is 45 to 75 per cent by weight and 15 to 20 per cent of this is extracellular, then the total volume of cell water is roughly two or two and a half times that in the extracellular space. There is no ready way of measuring the cell water directly, though the volume of distribution of tagged potassium, which is chiefly located within cells, does approximate such an index (6a, b).

## II. Electrolytes

The electrolytes in the body fluids which bear positive charges ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{++}$ ,  $\text{Mg}^{++}$ ,  $\text{H}^+$ ,  $\text{NH}_4^+$ ) are *cations*. The first four of these are also called, especially in the older reports, the fixed base of the body. This distinction is founded on the presumption that these particular elements cannot be manufactured or destroyed in the body, in contrast to the hydrogen and ammonium ion. The chief negative charged electrolytes, *anions*, or acids, consist of  $\text{Cl}^-$ ,  $\text{HCO}_3^-$ , protein, phosphates and an unmeasured fraction of organic and other acids referred to as  $\text{x}^-$ . Though sulfates are usually included in this list they are not routinely measured and the extent and significance of their variations in health and in disease have not been defined. These cations and anions are present in greater or lesser concentration in all of the fluids of the body. Actually in some tissues not all are represented. Thus calcium appears to be excluded from erythrocytes.

In general, clinical measurements are confined to samples of blood, serum

or plasma. There is no direct access to either the electrolytes of the interstitial space or of the cells, though, as has been indicated, indirect estimates of cellular contents with radioactive isotopes are possible in the living organism and in analyses of tissues.

#### *A. Reasons for Analyzing Serum or Plasma Electrolytes Rather than Whole Blood*

Analyses of serum or of plasma for electrolyte content are to be preferred to those of whole blood since the composition of electrolytes inside of blood cells is quite different from that in plasma. Hence alterations in the number or the size of the erythrocytes will obviously influence the analytic results and either mask or accentuate significant changes present in the plasma. This criticism is generally taken not to apply to solutes such as glucose, urea, and nonprotein nitrogen which are thought to be uniformly distributed and in the same concentrations in the water of plasma and of cells. A moment's reflection will indicate that this assumption is not valid because the water content of these two phases is quite different. The practice is universally continued however because in these latter instances the final differences are relatively small.

All specimens of blood should be drawn into a dry oiled syringe and introduced under oil into a centrifuge tube. The serum or plasma should then be separated promptly from the cells. This obviates hemolysis, prevents the escape or access of gasses, and minimizes transfers between cells and plasma.

#### *B. Milliequivalents, Millimols and Milligrams as Units of Solute Measurement*

The particular unit in which an analytic result is expressed is quite important in evaluating the anion-cation pattern of serum. For this purpose it is essential that the electrolytes of plasma or serum present in the higher concentrations be expressed in the same unit. Hence the milliequivalent is employed because it relates one ion to another in terms of its charge, valence, or combining power. This is necessary since the masses of the individual electrolytes are quite different, depending on their atomic weight. As a consequence a gravimetric unit such as a milligram cannot be used.

The milliequivalent is derived as follows: the electrical charge of one atomic weight, 1.0 gram, of hydrogen is used as the standard of reference; that amount of any other ion which can replace this amount of hydrogen, or combine with it, is an *equivalent* of 1.0 gram of hydrogen and  $\frac{1}{1000}$  of this amount is a *milliequivalent*. The unit "*milligram per cent*" can be converted to milliequivalents per liter by multiplying by 10 to express the original value in milligrams per liter, and dividing by the atomic weight and



multiplying by the valence. However, there is no reason why the standard solutions employed in the analytic technic, and hence the results, should not be set up directly in milliequivalents. This is now extensively though not universally practiced with regard to  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Cl}^-$  and  $\text{HCO}_3^-$ . These are the electrolytes whose concentrations must be known for the evaluation of the anion-cation, or acid-base, pattern of the body fluids. The last of these however is still often determined first as the total  $\text{CO}_2$  content of serum in terms of volumes per cent. The conversion from volumes per cent of  $\text{CO}_2$  to bicarbonate is readily made by multiplying by 0.423. This figure takes into account the  $\text{CO}_2$  and  $\text{H}_2\text{CO}_3$  in solution but assumes a normal pH.

In common practice the other electrolytes of serum, i.e., calcium, phosphorus, and protein are usually still expressed in gravimetric terms. There are justifiable reasons for this. First, in terms of milliequivalents, they contribute but little to the bulk of the anion-cation balance; moreover, the conversion of these particular components of serum or plasma to milliequivalents is complicated by the fact that the amount of calcium bound to protein can vary, that serum inorganic phosphorus can exist in a variety of ionic forms ( $\text{H}_2\text{PO}_4^-$ ,  $\text{HPO}_4^{=}$ , and  $\text{PO}_4^{=}$ ), and that the ionization of serum proteins as anions is influenced by the pH of the solution and probably by the concentration and the composition of the serum proteins themselves.

The term millimol is oftentimes used in place of milliequivalent. This unit does not take into account the combining power of the ion. In the case of univalent ions the milliequivalent and millimol values are the same; with bivalent ions however the millimol concentration will be only one-half of the milliequivalent value.

### III. Electrolyte Concentrations in Health

It is highly desirable to have suitable standards of reference available as an aid to deciding whether a value in a particular patient is abnormal. Obviously with gross deviations such values are in a sense superfluous. However in all other instances control data obtained in one's own laboratory or in other laboratories with comparable analytic technics are indispensable. Particular care must be taken to ascertain that the age and sex of the controls are comparable and that the specimens are obtained under conditions which are uniform. For this latter purpose blood is usually withdrawn following an overnight fast, and preferably while the subject or the patient is still abed. Particular care must be taken to avoid venous stasis in drawing the sample under oil, and in separating the serum from the cells within a reasonably prompt period of time.

These principles have been followed in obtaining the control data which follow. It is to be noted that the concentration of certain electrolytes varies



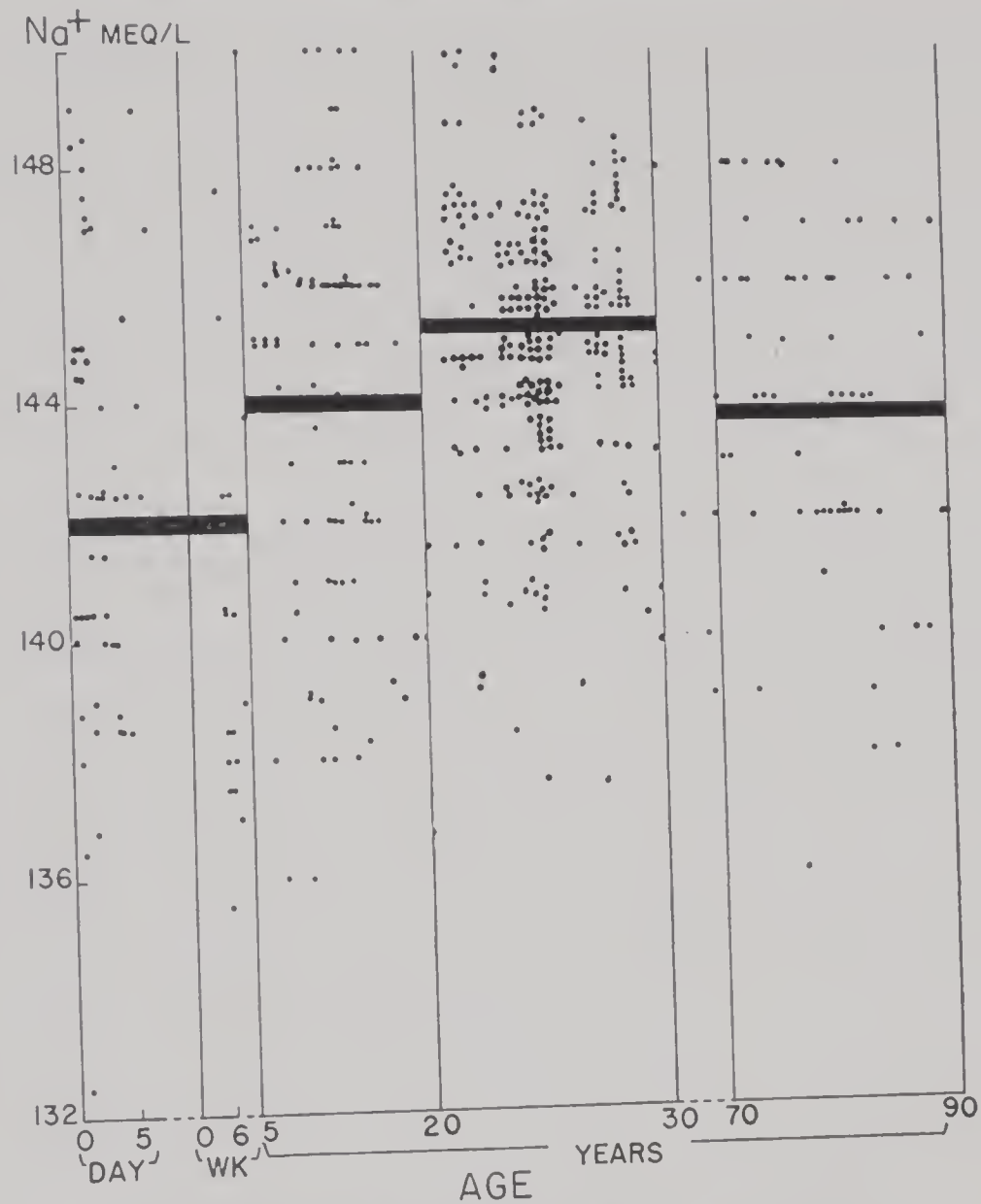


FIG. 4-1. AVERAGE SERUM SODIUM VALUES IN HEALTH

Above data represent analyses on newborn infants, boys and girls in a well run home for children, on healthy young adults, and on inmates of two homes for the aged who were apparently well. The mean value (horizontal bar), and standard deviation, on these four groups were, in the order named:  $143 \pm 3.3$  mEq. per l.;  $144 \pm 3.0$ ;  $146 \pm 2.6$ ;  $144 \pm 3.2$ . (Danowski *et al.*, unpublished data on flame photometry.)

with age and sex and that the so-called fasting state is not characterized by a constancy of the serum electrolytes.

Figure 4-1 presents the serum sodium values in newborn infants, in growing children, in healthy young adults, and in apparently healthy old men and women. Several points are deserving of comment. First, it is evident that, in general orders of magnitude, the four groups are not identical insofar as the concentration of sodium is concerned. Second, the scattering is greatest in the newborn infant group. Finally, it is clear that sodium levels as low as 136 are only rarely encountered in health irrespective of age.

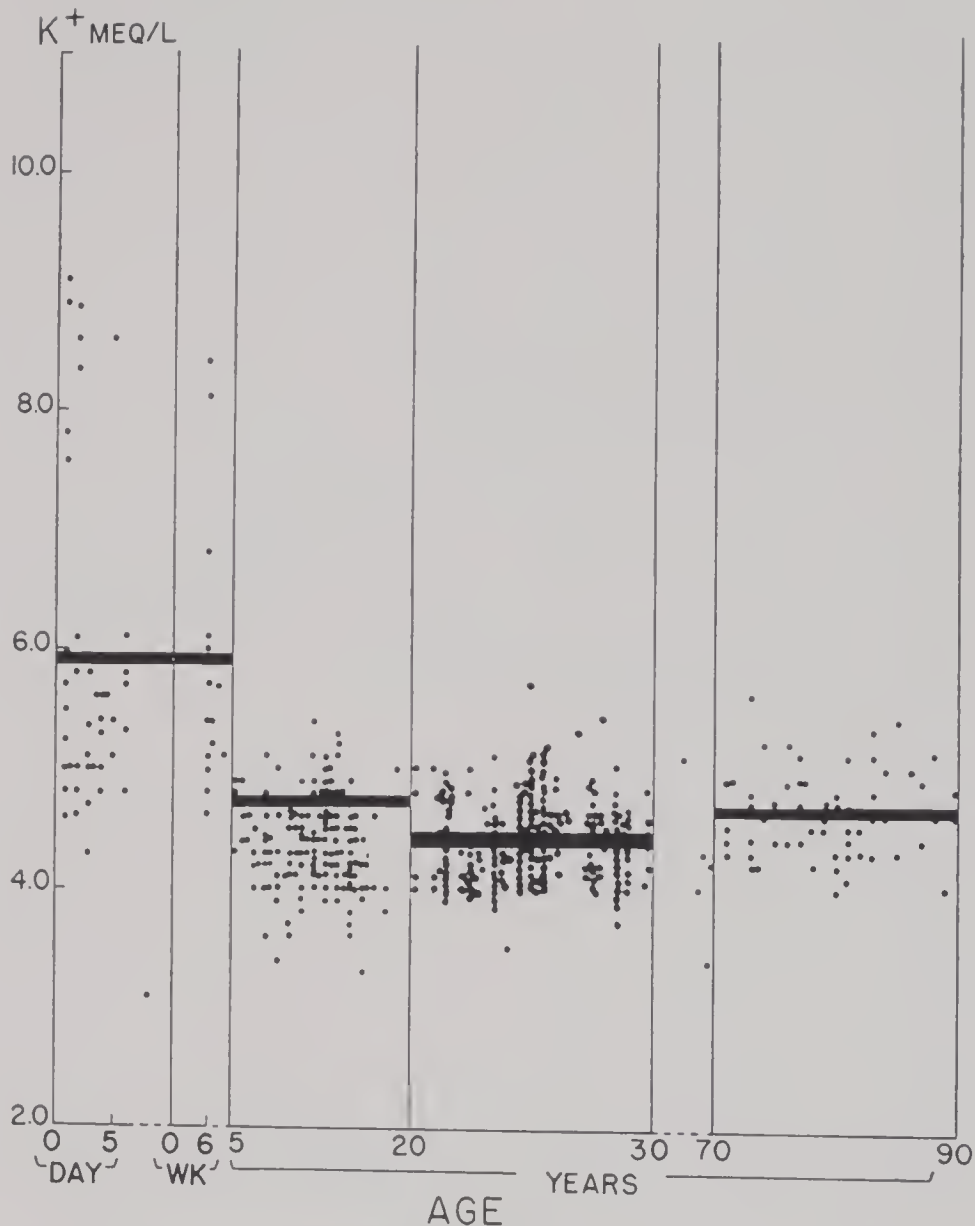


FIG. 4-2. AVERAGE SERUM POTASSIUM VALUES IN HEALTH

The mean value and the standard deviation for each of the age groups shown in the above figure were:  $5.9 \pm 1.4$  mEq. per l. in infants;  $4.3 \pm 0.4$  in children;  $4.4 \pm 0.3$  in young adults; and  $4.6 \pm 0.4$  in old men and women. (Danowski *et al.*, unpublished data on flame photometry.)

The control serum potassium values in figure 4-2 indicate that the newborn infant may have distinctly high concentrations. Beyond infancy the range is narrowed with an upper limit of 5.6 and a lower of 3.2 milliequivalents per liter.

The calcium values in figure 4-3 indicate that this element is present in quite comparable concentrations from birth on with a rise in old age.

We have no values for the serum magnesium in health. The range reported from other laboratories is 1.3 to 2.5 milliequivalents per liter (7a-e), but the distinct limitations in the analytic technics employed for this determination must be kept in mind.

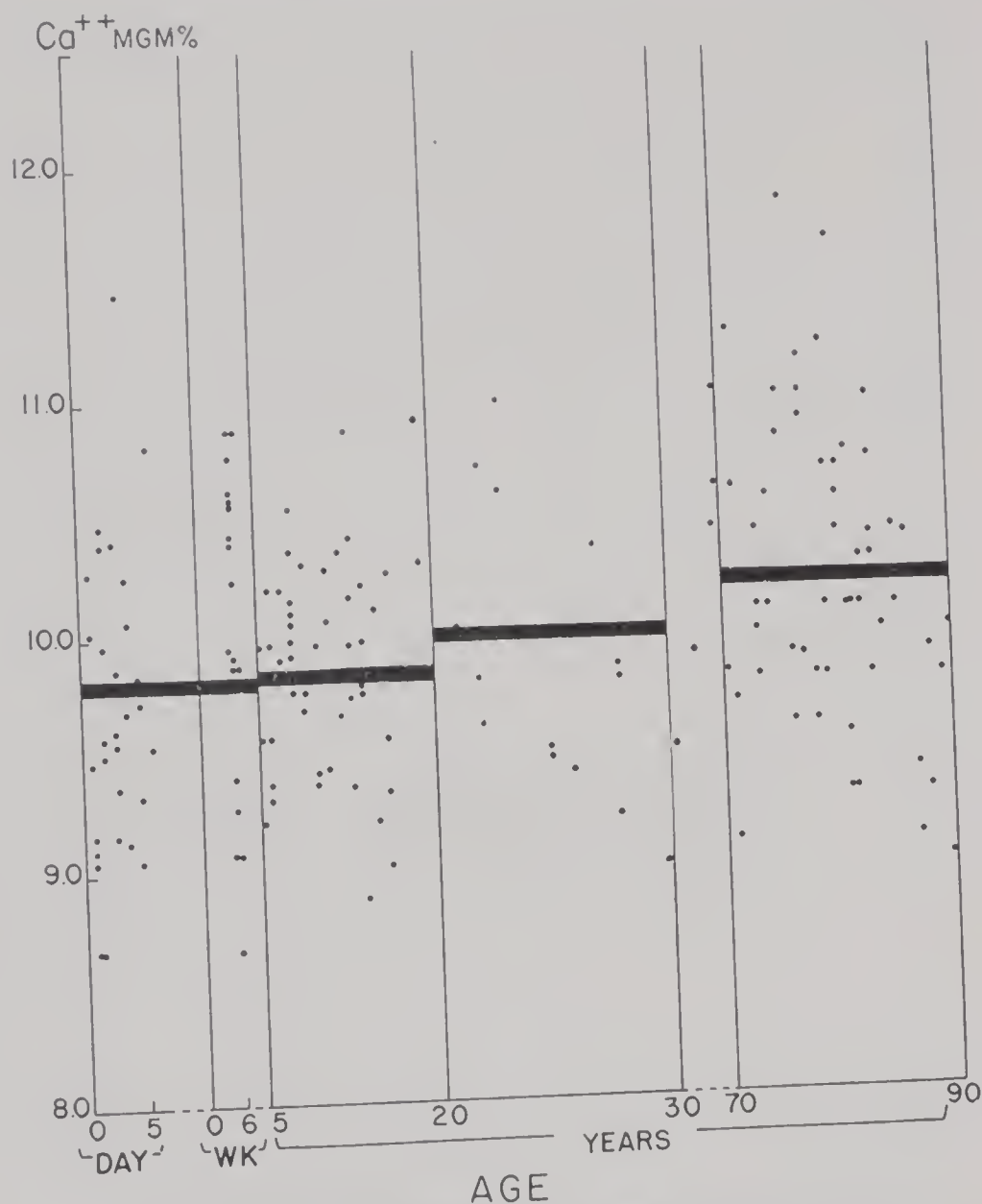


FIG. 4-3. AVERAGE SERUM CALCIUM VALUES IN HEALTH

In newborn infants the mean and standard deviation were found to be:  $9.8 \pm 0.7$  mg. per cent; in children:  $9.8 \pm 0.4$ ; in young adults:  $10.0 \pm 0.6$ ; in aged men and women:  $10.3 \pm 0.7$ . (Danowski *et al.*, unpublished data based on Tisdall's simplification of the Kramer-Tisdall method.)

Insofar as the anions are concerned our data indicate that the mean serum bicarbonate and chloride values are again not the same in these four age groups and that in addition sex differences are present in at least the healthy young adults. These findings are shown in figures 4-4 and 4-5 and are in keeping with the data of others (8a, b). In children the mean serum bicarbonate value is 23.1 milliequivalents per liter and the chloride is 103.3, and no sex difference appears evident, though the observations are limited. In healthy young adults the serum bicarbonate is higher in the males than in the females while the opposite relationship holds with respect to chloride.



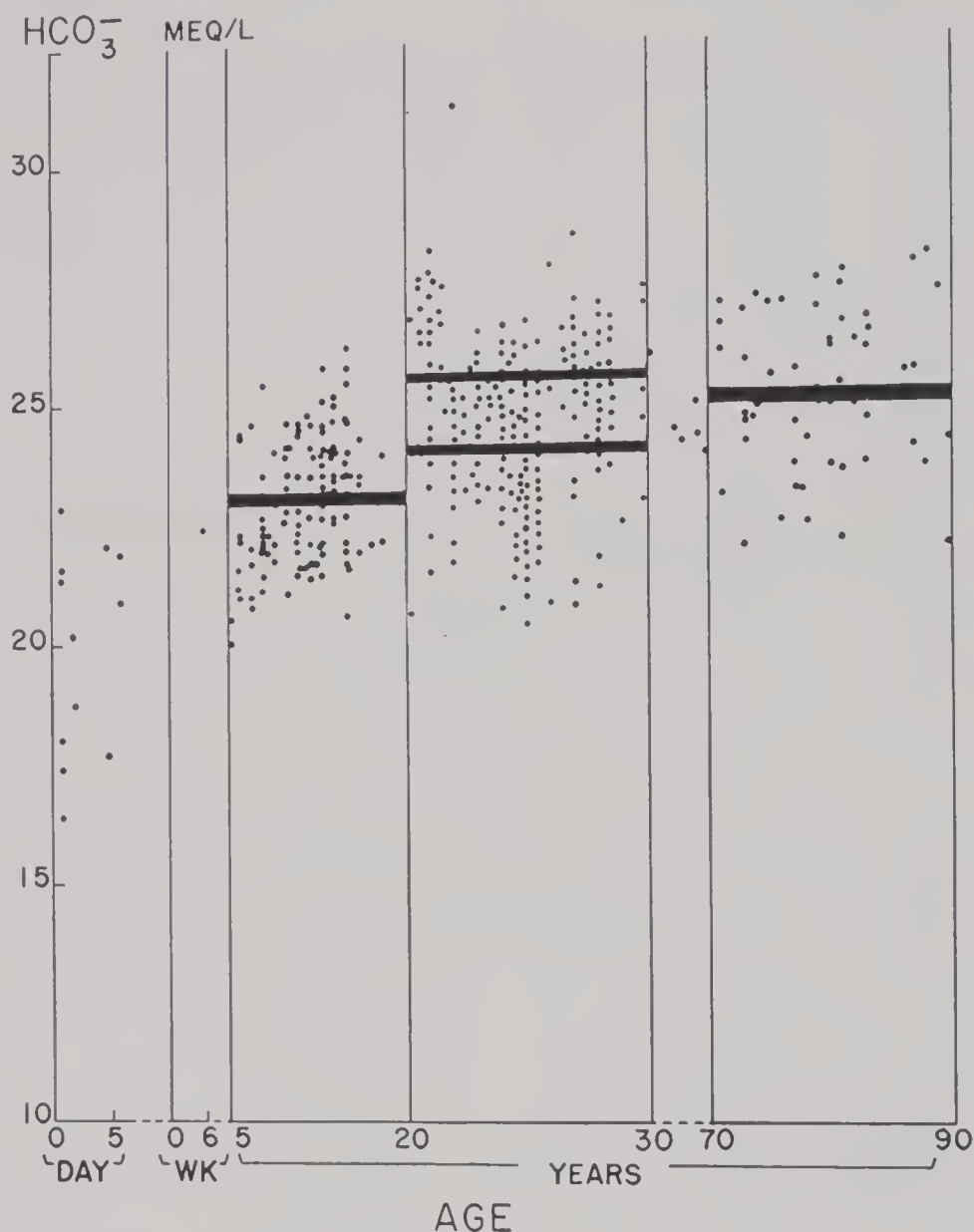


FIG. 4-4. AVERAGE VALUES FOR TOTAL SERUM  $\text{CO}_2$  CONTENT EXPRESSED AS BICARBONATE

In healthy children the mean value is:  $23.1 \pm 1.3$  mEq. per l. Healthy young men and young women showed differences which were statistically significant:  $25.6 \pm 1.3$  and  $24.0 \pm 1.6$ , respectively. In aged patients the mean and standard deviation were  $25.0 \pm 2.0$ . (Danowski *et al.*, unpublished data.)

Our data are as yet insufficient to determine whether this sex difference is or is not still present in old age. The newborn infant on the other hand usually has a very low bicarbonate and a high chloride when contrasted with any of the other three groups. Our own figures on this point are scanty but are in line with those from other laboratories (9a-e).

Serum inorganic phosphorus values vary with age in contrast to the relative stability of the serum calcium concentrations in healthy subjects. They are highest shortly following birth and then gradually decline through

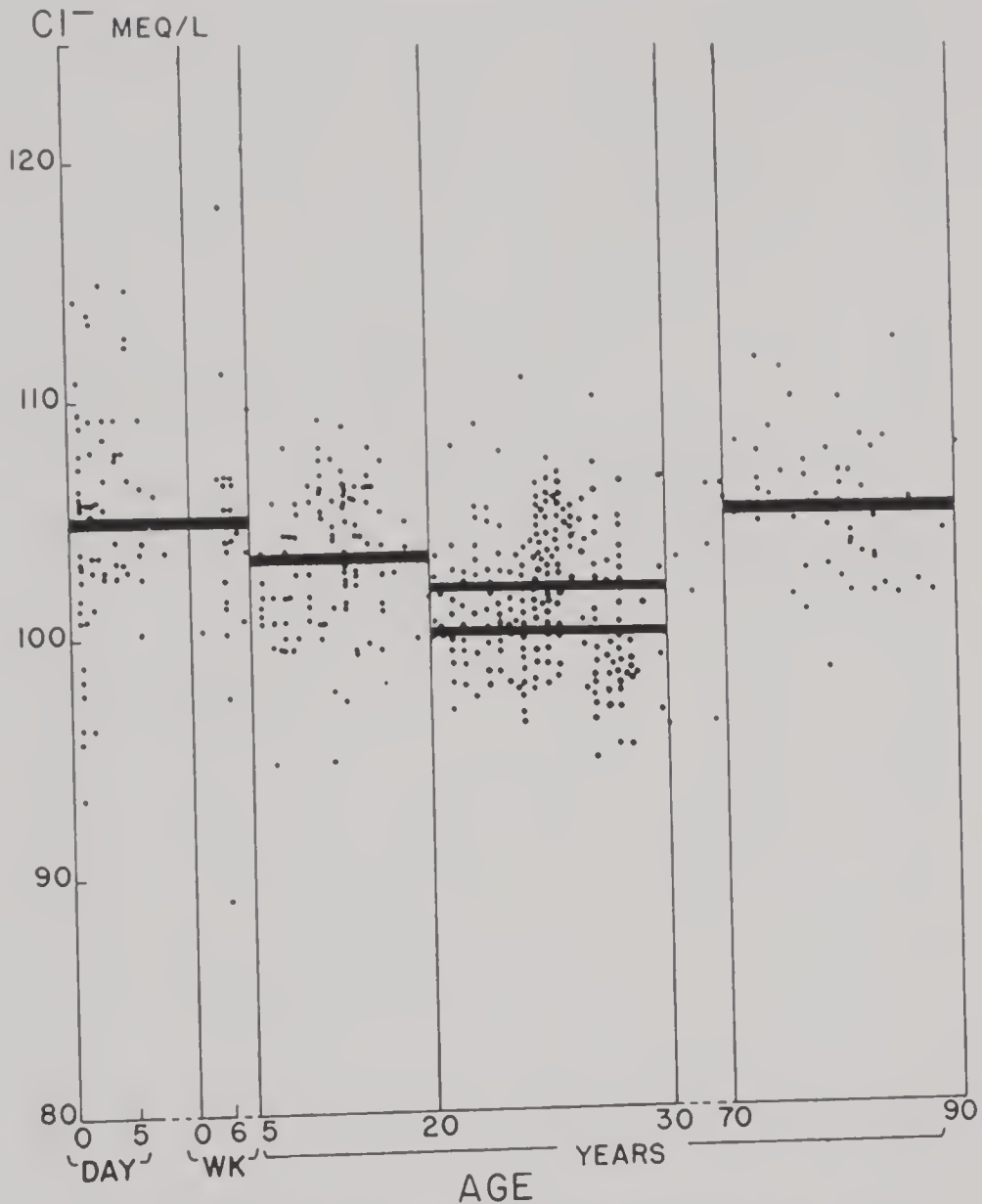


FIG. 4-5. SERUM CHLORIDE CONCENTRATIONS: AVERAGE VALUES IN HEALTH

Values are highest in newborn infants, averaging  $104.9 \pm 4.7$  mEq. per liter. In healthy children the mean was  $103.3 \pm 3.0$ . As in the case of total  $\text{CO}_2$  content or bicarbonate, a sex difference is present in healthy young adults: males averaged  $100.2 \pm 2.4$  and females  $102.3 \pm 2.9$ . In the aged population the mean value was found to be  $105.3 \pm 3.0$ . (Danowski *et al.*, unpublished data based on the Volhard titration.)

childhood and adulthood reaching their lowest levels in extreme old age (fig. 4-6).

Newborn infants have albumin and globulin levels which are lower than those of older children or adults (figs. 4-7 and 4-8). This obviously means that their total serum protein levels are also lower (fig. 4-9). These differences have also been reported by others (10a-d).

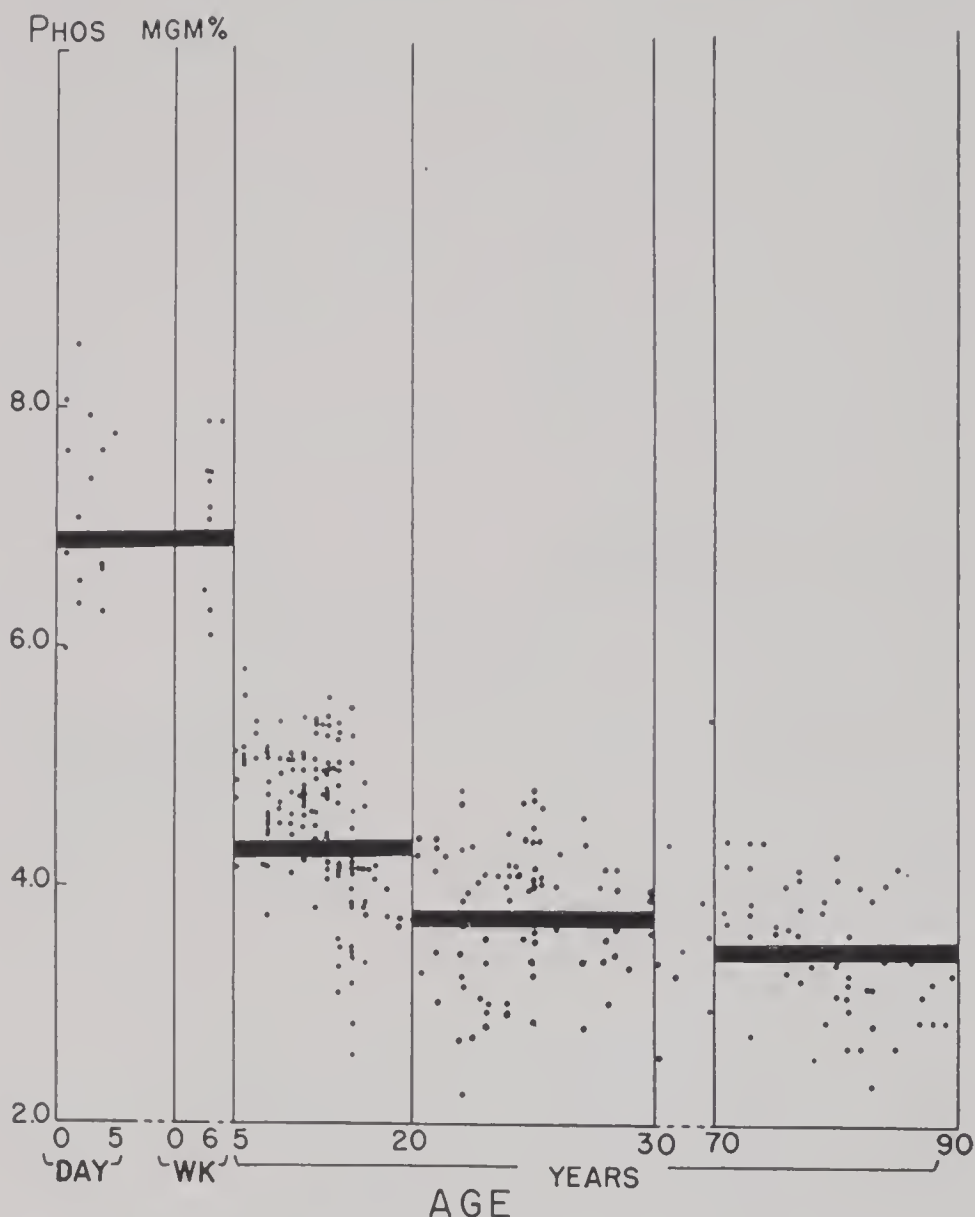


FIG. 4-6. SERUM INORGANIC PHOSPHORUS IN HEALTH

The mean concentrations fall progressively with age. Thus in newborn infants:  $6.88 \pm 1.57$  mg. per cent; in children up to 12.5 years of age:  $4.76 \pm 0.41$ ; in children 12.5 to 18.0 years of age:  $4.34 \pm 0.69$ ; in young adults:  $3.96 \pm 0.46$ ; and in old people:  $3.47 \pm 0.56$ . (Danowski *et al.*, unpublished data based on an adaptation of the Fiske-Subbarow procedure to the photoelectric colorimeter.)

#### IV. Constancy of the Fasting Values of Serum Electrolytes

Measurements of various serum components on different days in healthy children in the same state with respect to fasting, activity, etc. reveal variations in excess of the analytic limitations of the method. This is clearly shown in the diagram based on studies in healthy children which makes up figure 4-10. Similar fluctuations are seen in two healthy adults, figure 4-11, together with the sex difference in  $\text{CO}_2$  and chloride. It is im-



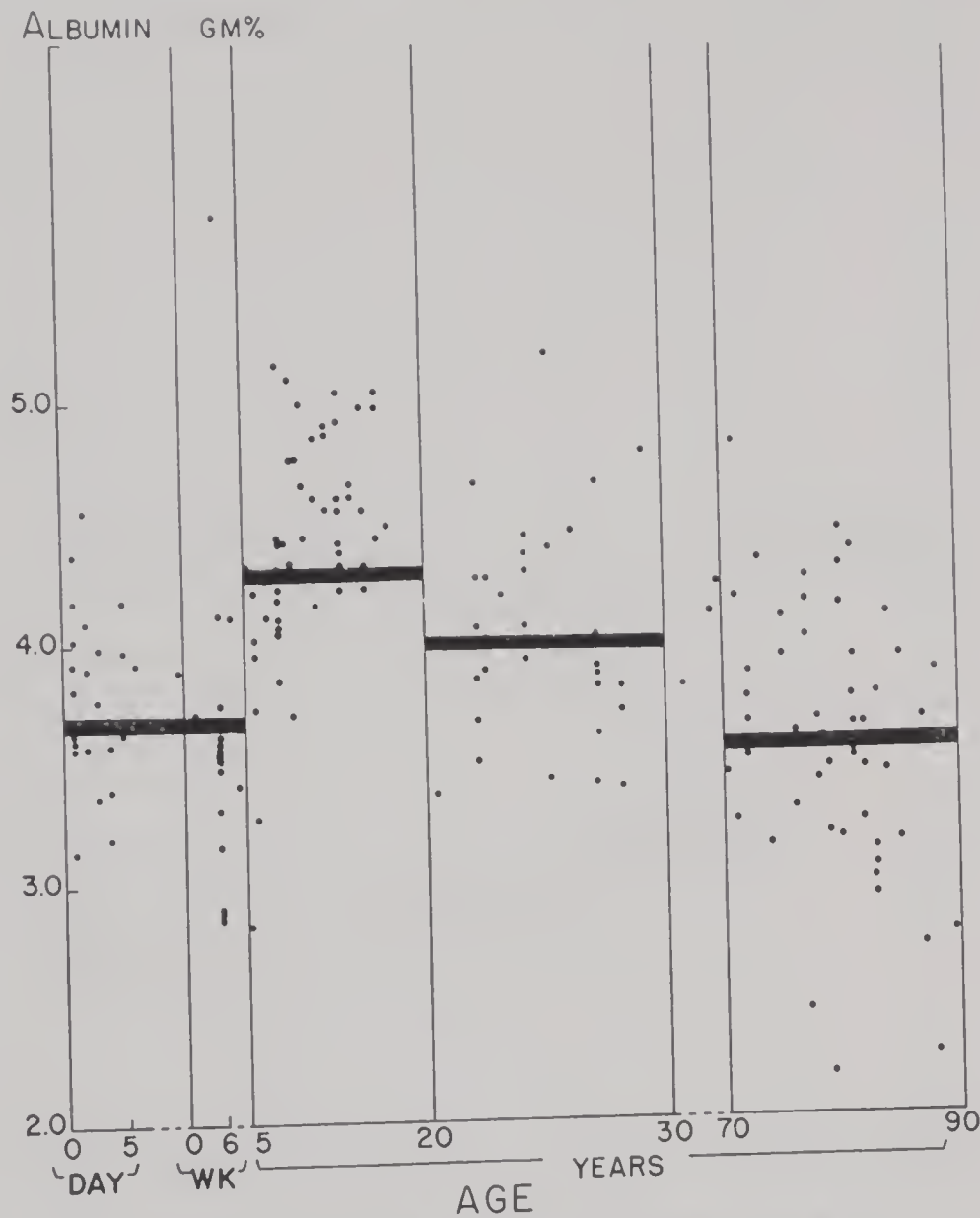


FIG. 4-7. SERUM ALBUMIN CONCENTRATION

The lowest values were present in newborn infants:  $3.68 \pm 0.39$  grams per cent; in children:  $4.28 \pm 0.58$ ; in young adults:  $4.16 \pm 0.33$ ; in old adults;  $3.61 \pm 0.54$ . (Danowski *et al.*, unpublished data based on sulfate separation method of Majoor and macro Kjeldahl nitrogen (3a).)

portant to recognize the existence of these day to day fluctuations and these sex differences if false interpretations of the effects of therapeutic or experimental procedures are to be avoided.

In this regard it is of interest to point out that the serum constituents vary during the fasting state even when examined at intervals during the same morning. Thus, with the passage of time following awakening, and despite continued bed rest, the serum bicarbonate tends to increase while the phosphorus and potassium fall. This is shown in figure 4-12. Hence the

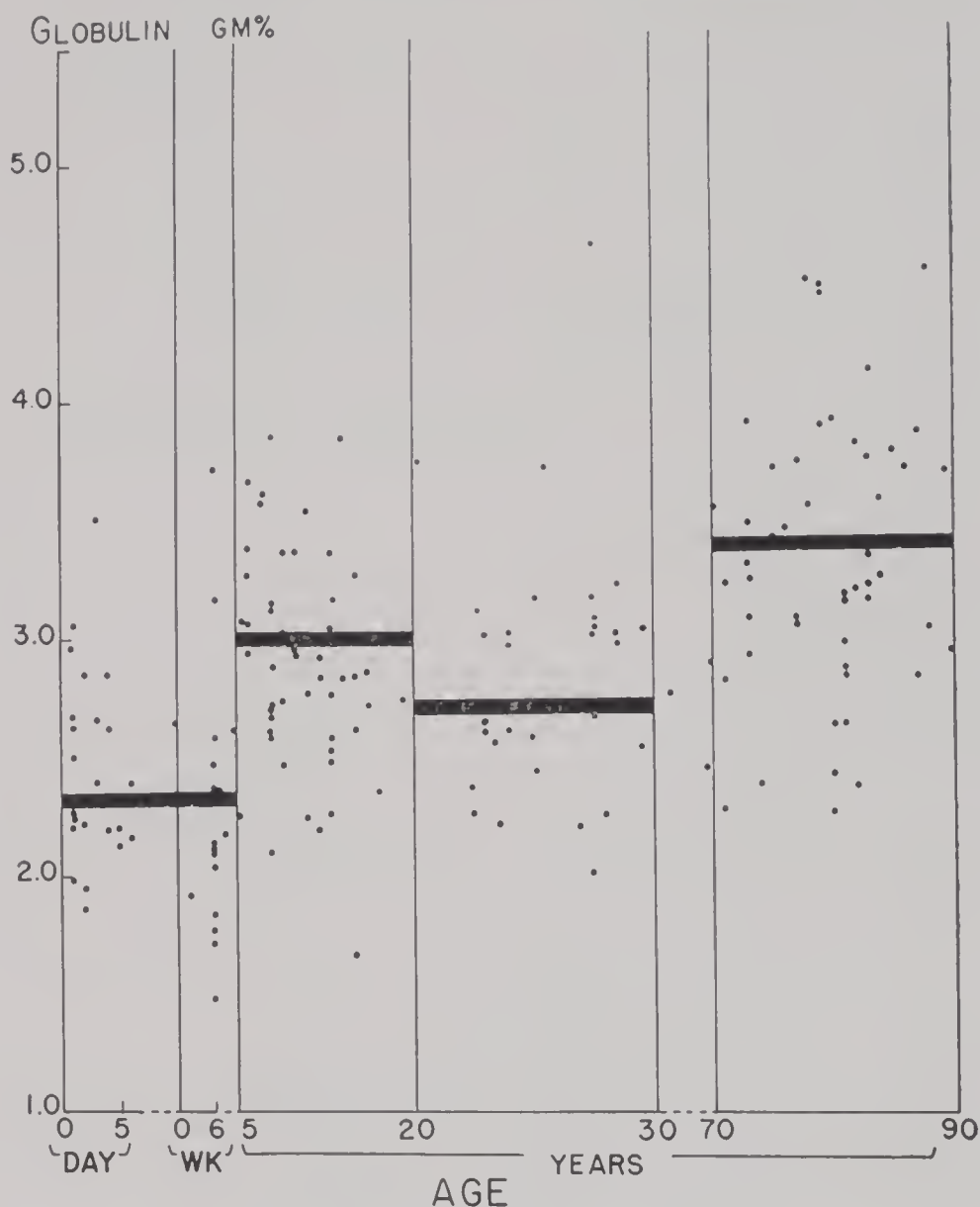


FIG. 4-8. SERUM GLOBULIN CONCENTRATION

The lowest values again were present in newborn infants:  $2.33 \pm 0.41$  grams per cent; in children:  $3.00 \pm 0.55$ ; in young adults:  $2.83 \pm 0.27$ ; and in older adults:  $3.34 \pm 0.64$ . (Danowski *et al.*, unpublished observations based on method of Majoor (3a).)

stability of the serum constituents is relative and not absolute. In other words the oscillations of a steady state, as described in chapter 1, are again evident.

From the data given above we can construct the following composite graphs or Gamble diagrams of the anions and cations in the sera of these four groups of healthy subjects (fig. 4-13).

To obtain values in interstitial fluid we must apply corrections for the lower colloid and greater water content in the nonplasma portion of the extracellular fluid. This necessitates separate sets of corrections for the

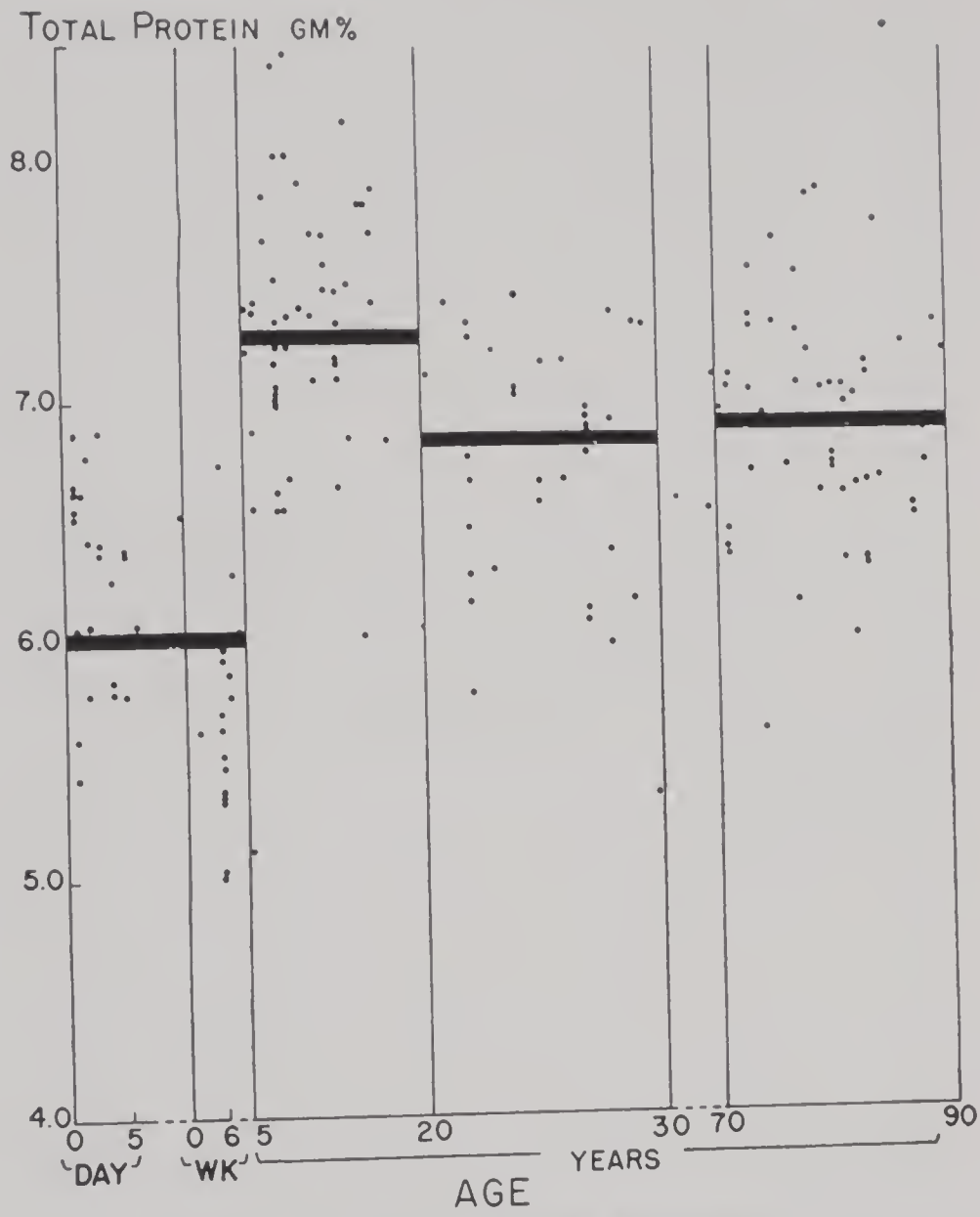


FIG. 4-9. TOTAL SERUM PROTEINS

Newborn infants  $6.01 \pm 0.52$  grams per cent; children  $7.27 \pm 0.57$ ; young and old adults  $6.99 \pm 0.29$  and  $6.95 \pm 0.61$ , respectively. (Danowski *et al.*, unpublished observations based on method of Major (3a).)

anions and cations because of the Donnan effect of the serum proteins. Formulae A and B provide illustrative examples:

$$\frac{\text{Cl}^- \text{ of Serum}}{0.95 \times \text{H}_2\text{O of Serum}} = \text{Cl}^- \text{ of interstitial fluid (A)}$$

$$\frac{\text{Na}^+ \text{ of Serum} \times 0.95}{\text{H}_2\text{O of Serum}} = \text{Na}^+ \text{ of interstitial fluid (B)}$$

These calculations raise the value of each of the components principally because the removal of the protein from the serum or plasma makes room



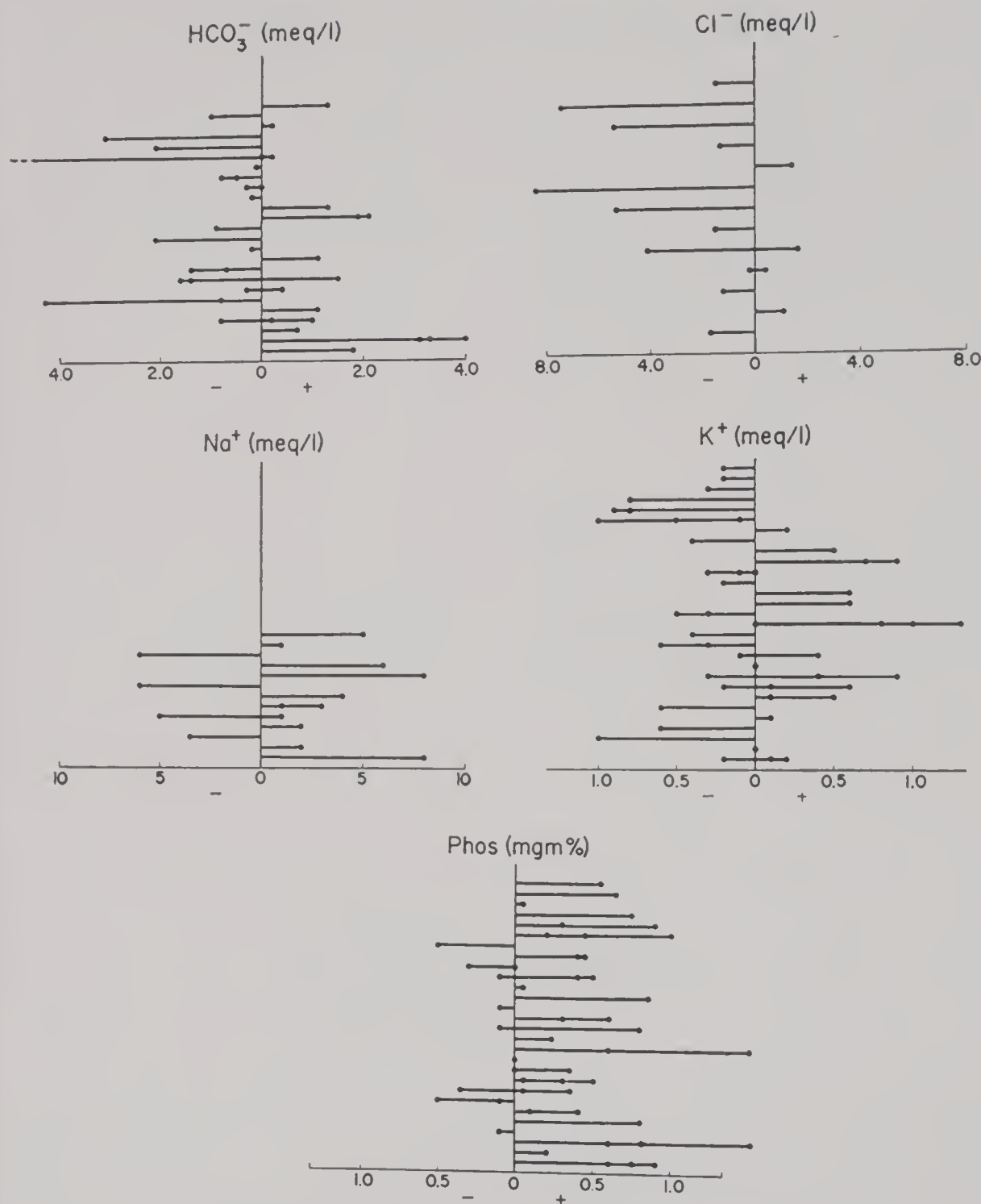


FIG. 4-10. DAY TO DAY FLUCTUATIONS IN THE SERUM ELECTROLYTES OF HEALTHY CHILDREN

The points on each line represent variations from an initial value in the same individual as measured on different, not successive days. However, the position of the point on the line does not indicate the sequence of the samples. The samples of sera were always obtained under the same conditions: the children were fasting and at bed rest.

The fluctuations represent oscillations of the steady state and are attributable to unidentified factors other than fasting and bed rest.

In this small series the maximal day to day fluctuations in the measured constituents were found to be: more than 4 mEq. per liter in HCO<sub>3</sub>, 8 mEq. per liter in Cl and Na, 1.3 mEq. per liter in K, and 1.5 mg. per cent in serum inorganic phosphorus. (Danowski *et al.*, unpublished data.)

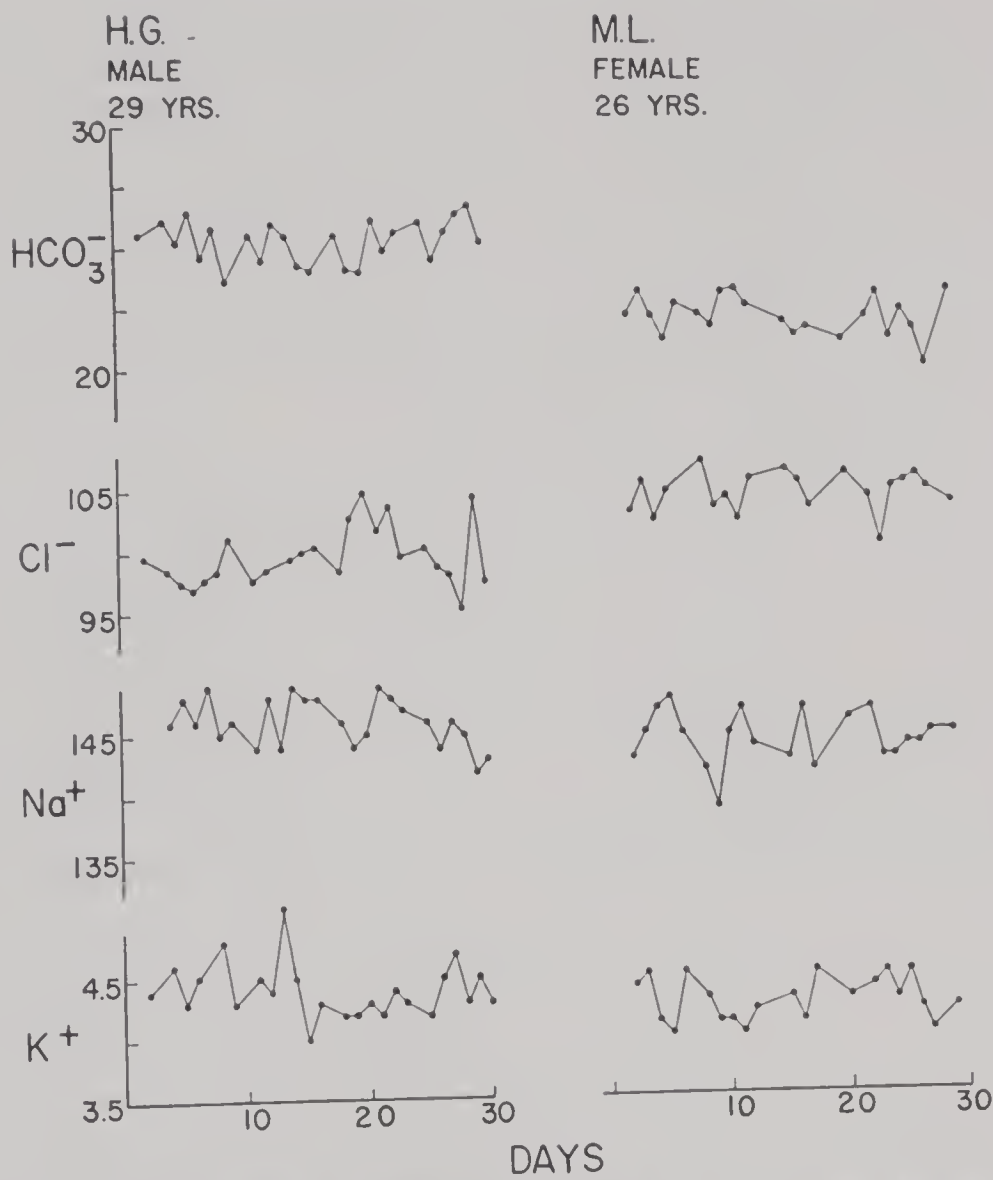


FIG. 4-11. SERIAL MEASUREMENTS OF SERUM ELECTROLYTES IN HEALTHY ADULTS

The day to day oscillations in the fasting serum levels of electrolytes in two ambulatory healthy adults are in keeping with the finding in healthy fasting children at bed rest shown in fig. 4-10. In addition the sex differences in serum chloride and bicarbonate are clearly shown: in the male the chloride was lower and the bicarbonate higher than in the female. (Danowski *et al.*, unpublished data.)

for a larger amount of H<sub>2</sub>O and of solutes in a given aliquot of this solution. This is shown in figure 4-14.

The diagram illustrating the water and electrolyte composition of cells can be drawn most readily for the cells of blood. Thus analyses of whole blood and of serum together with a knowledge of the hematocrit permits calculation of the probable cell content. This is shown in part in figure 4-15. It is to be noted that there is much more potassium and less sodium in blood cells than in whole blood, plasma or serum, and that in the case of the blood cells calcium appears to be entirely excluded.

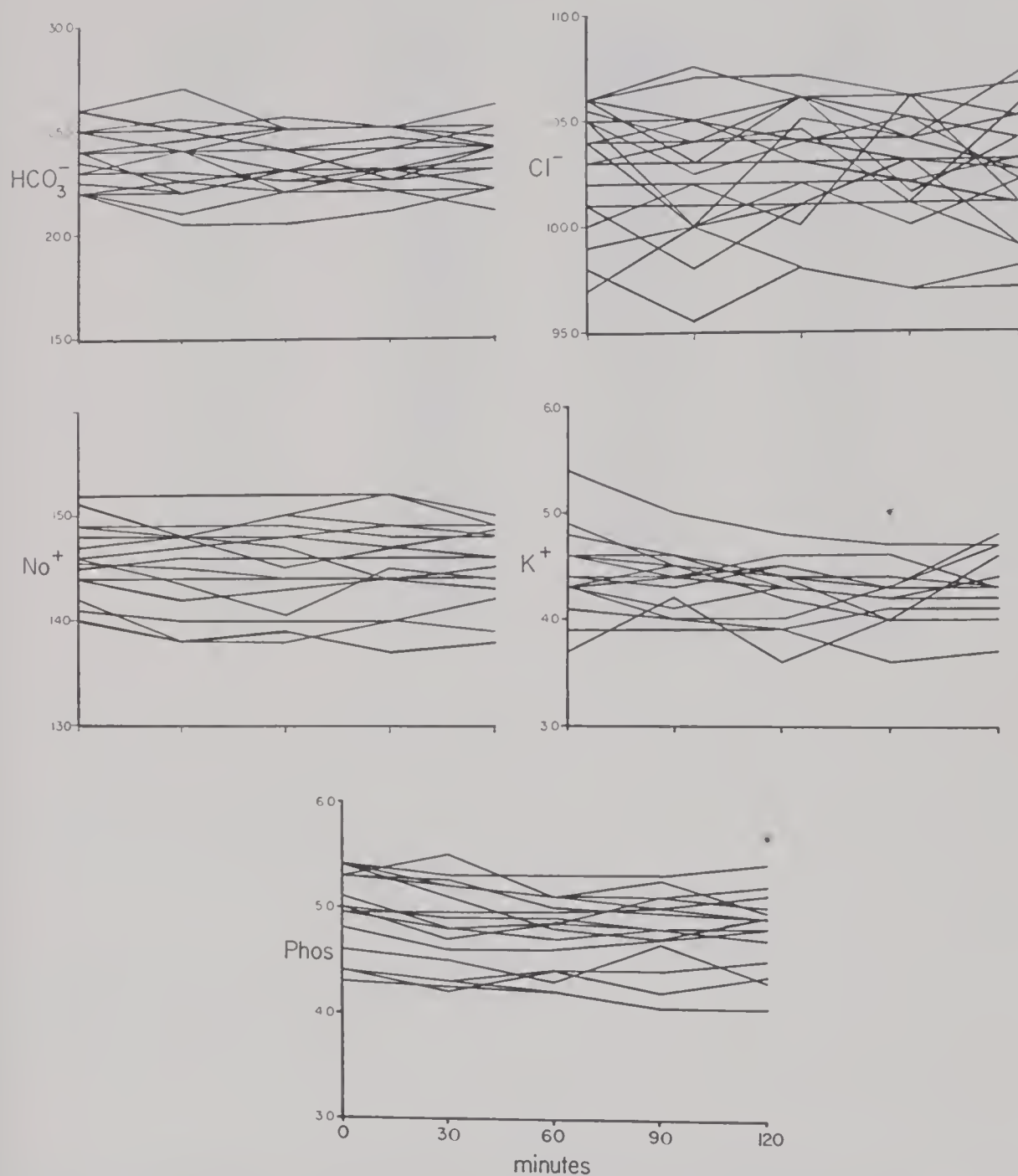


FIG. 4-12. THE RELATIVE CONSTANCY OF ELECTROLYTES IN FASTING CHILDREN AT BED REST

Each curve depicts successive fluctuations in one subject during the indicated time intervals.

It is readily evident that the serum values fluctuate under these conditions as they do in the day to day determinations. In addition one can demonstrate a cumulative effect in that ultimately a statistically significant decrease in serum potassium and in serum phosphorus appeared. These points are indicated by asterisks. (Danowski *et al.*, unpublished data.)



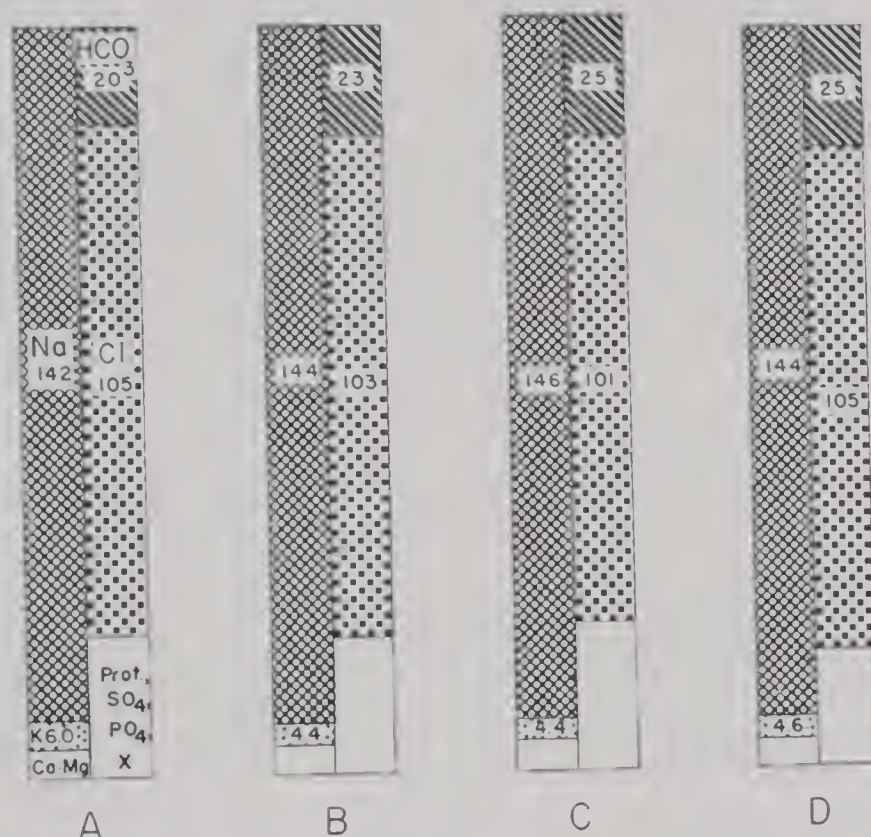


FIG. 4-13. MEAN VALUES FOR THE CHIEF ANIONS AND CATIONS IN THE SERA OF GROUPS OF HEALTHY SUBJECTS

The similarities and the differences among the average values for the serum sodium, potassium, bicarbonate, and chloride are shown for groups of newborn infants (A), healthy children (B), healthy young adults without regard to sex (C), and apparently healthy inmates of two homes for the aged (D). (Based on data in fig. 4-1, 4-2, 4-4, 4-5.)

Comparable calculations based on analyses of fat-free tissue permit estimates concerning the electrolyte content of muscle cells as shown in figure 3-1. As has been pointed out in chapter 3, analyses of various tissues indicate that cellular composition is by no means uniform.

## V. The Osmotic Pressure of Body Fluids

The osmotic pressure of any solution is dependent upon the number of particles in solution irrespective of whether they are ionized or unionized. Hence in the body all of the electrolytes as well as the nonelectrolytes contribute to the osmotic pressure. However in dealing with certain physiologic effects we are concerned only with those solutes which cannot freely traverse the cell membranes and thereby give rise to a differential osmotic pressure. It is pertinent in this regard that the cells are the particular domain of potassium as is the extracellular fluid in the case of sodium. Hence losses or gains of one or the other of these body constituents inevitably alter the osmotic pressure in the particular compartment involved, assuming that

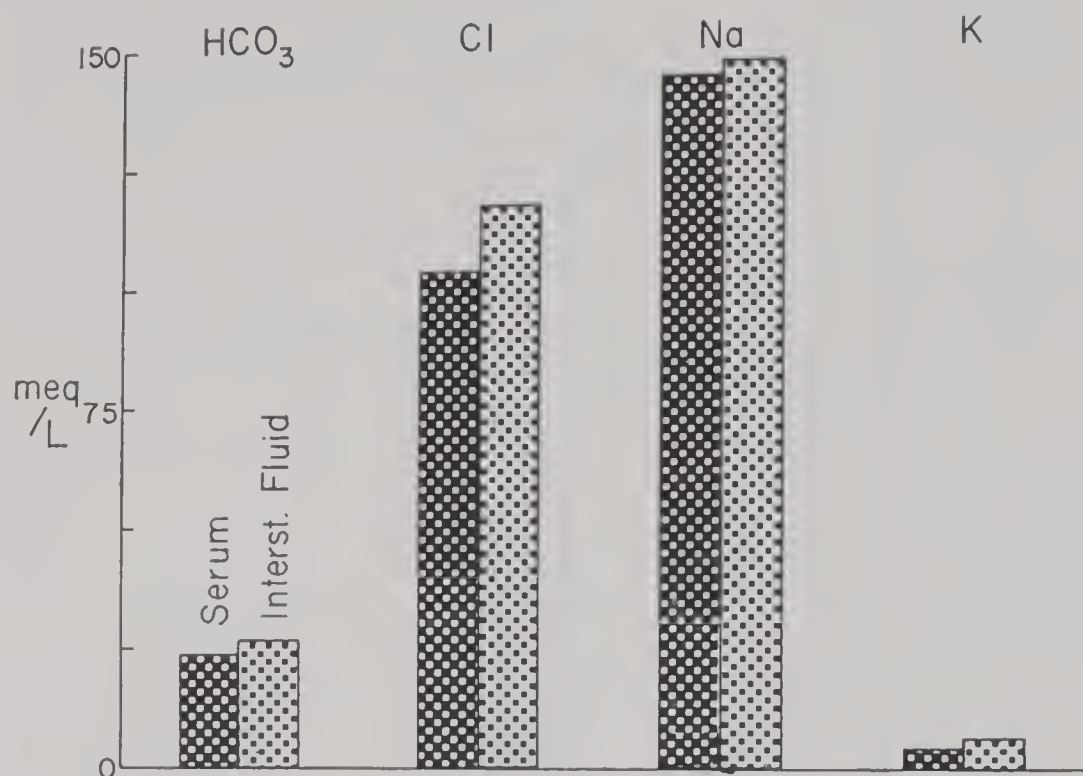


FIG. 4-14. ELECTROLYTES OF INTERSTITIAL FLUID

Dark columns refer to concentrations in serum; light columns depict interstitial fluid.

The mean serum values for the various age groups shown in fig. 4-13 have been converted into concentrations present in interstitial fluid, using a value of 0.930 gram per liter for serum water and a Donnan factor in accordance with the formulae presented in the text. (Based on data in fig. 4-13.)

the osmotic activity of cell solutes remains constant. This in turn induces transfers of water across the cell membrane from the solution of lower osmotic pressure to that which is greater.

## VI. Serum Constituents as an Index to the General State of the Body Fluids

It has been pointed out that clinicians and experimentalists have a direct approach only to the plasma and serum electrolytes. However certain general properties of body fluids permit estimates of the probable concentrations and the osmotic activity of solutes in the other compartments.

The first of these is the universal permeability of water, i.e., water will enter or leave any of the body fluid compartments in response to osmotic pressure changes until the osmotic pressures on the two sides of the separating membrane are the same. It naturally follows that the finding of a low osmotic pressure or hypotonicity in plasma inevitably means that it is also low within interstitial fluid and within cells. Similarly hypertonicity present in serum or plasma reflects a universal rise in osmotic pressure.

The second of these is the tendency for body water and solutes to remain

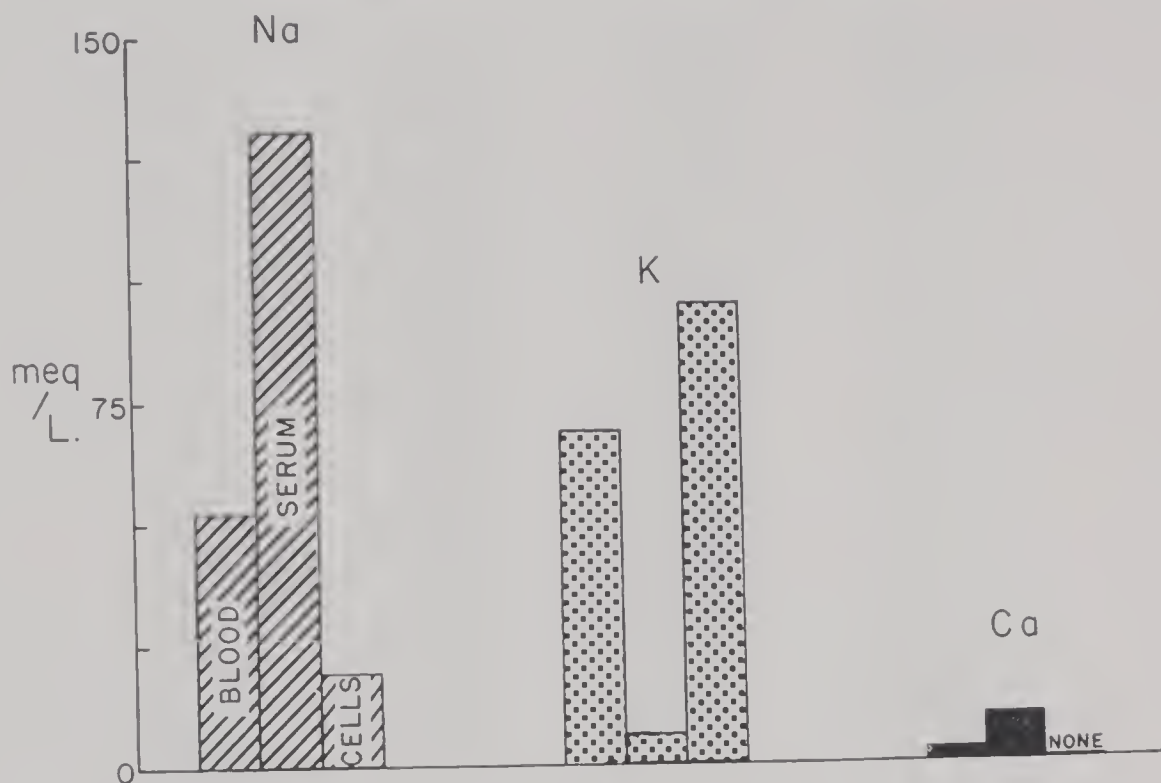


FIG. 4-15. ELECTROLYTES IN SERUM AND IN CELLS OF WHOLE BLOOD

Venous blood was obtained from S. D., a 45-year-old male with pulmonary fibrosis and polycythemia. Hematocrit levels averaged 71 volumes per cent. It is obvious that calcium is virtually excluded from cells while potassium is the chief cellular cation. Sodium predominates in plasma but is also present to a much lower extent within the cells.

This figure illustrates why it is important to measure electrolytes in serum or plasma rather than in whole blood. It is obvious that with the high hematocrit whole blood values for potassium would be unduly high while sodium would be below. (Danowski *et al.*, unpublished studies.)

constant in health despite wide variations in intake. These homeostatic mechanisms appear to be attuned to the maintenance of concentrations at the expense of volume in the early phase of the development of an excess or deficit. In the later phases concentrations are sacrificed for the sake of volume. Hence in patients in whom the history or physical findings indicate a change in the *total amount* of water or electrolytes, a normal *concentration* suggests that the disturbance is not as pronounced as it is when the concentrations are abnormal. However, it must be kept in mind that a single determination of the serum concentration of an electrolyte gives little physiologic information in itself because of the fairly extensive range of normal values. Thus, a value in the lower range of normal could be considered a "low normal" or could represent a clinically significant lowering of the concentration. It must therefore be interpreted in the light of other information. The term "interpretation" is used advisedly because, in the absence of measurements of *volume*, determinations of *concentration* give no direct knowledge of the *total amount* of the solute in question. For this reason



concentrations of electrolytes as determined in serum have to be interpreted in light of the clinical history and physical findings in the patient, the pathological physiology of the disease, if the latter is known, and the immediate prior fluid balance or fluid therapy of the patient (11).

**SUMMARY:** The water of the body is derived largely from the dietary intake and, to a lesser degree, from the combustion of foodstuffs. The proportion of body weight present as water varies from 45 to 75 per cent, depending upon the amount of body fat. The ratio between cell water and extracellular water is approximately 2 to 1. Since the osmotic pressure is equal inside and outside of cells, analyses of serum for water and electrolytes such as sodium, potassium, chloride, etc. will often reflect alterations in the water or electrolytes of the body. The concentrations encountered in health under fasting conditions provide standards of reference for the detection of changes in disease states. Concentrations by themselves however do not tell us about the total amounts of any particular constituent.

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## *Chapter 5*

# **MECHANISMS WHICH GUARD THE VOLUME AND COMPOSITION OF THE BODY FLUIDS IN HEALTH**

An adequate intake of water and of electrolytes is essential for the maintenance of body fluids within normal limits. It would appear that in health an intake of water and solutes is provided which is in excess of the body's actual needs and that metabolic and regulatory mechanisms then determine retention and excretion.

### **I. Factors Regulating Body Water Volume**

#### *A. Losses of Water Via Lungs, Skin and in Stools (table 5-I)*

Under ordinary conditions the adult each day loses some 800 to 1200 cc. of water via the skin and lungs (1a-e). This is commonly referred to as the insensible loss, since it involves the conversion of water directly into the gaseous phase. The energy for this process is derived from the heat of the body and conversely this process effectively disposes of some 25 per cent of the body's daily output of heat. This is therefore an obligatory and inescapable loss of body water, even though its magnitude may alter, as we shall subsequently see, with certain physiologic and disease states. Ordinarily such insensible losses of water from the body are thought to occur without concomitant output of electrolytes. Studies of skin surface washings however indicate that electrolytes and nitrogen may leave the body via this route without detectable sweating. This is surely in part at least a manifestation of desquamation, but the possibility that it is related to insensible water loss cannot be excluded. Sweat itself of course does contain definite amounts of electrolytes and nitrogen and hence in its presence not only is the loss of body water through the skin increased, often several fold, but this increase is also accompanied by electrolyte and nitrogen losses (2a-f).

TABLE 5-I. NORMAL ROUTES OF INTAKE AND OUTPUT OF WATER: APPROXIMATE VOLUMES IN HEALTHY ADULTS

NORMAL ROUTES OF INTAKE AND OUTPUT OF WATER: APPROXIMATE VOLUMES IN HEALTHY ADULTS			
Water drunk	1200 ml.	Urine	1500 ml.
Water in food	1000 ml.	Stool	100 ml.
Water of oxidation	300 ml.	Insensible water	900 ml.
	2500 ml.		2500 ml.

The only other nonrenal loss of body water which occurs in health is the small amount present in formed stools.

### *B. Urinary Output of Water*

The daily urinary output of water then strikes a balance between the extrarenal water losses and the daily supply of water from food and fluids as well as from that derived by combustion of foodstuffs. In other words the volume of urine is dependent upon the water and solute loads which remain following any extrarenal output which may be occurring. The magnitude of the output is determined by receptors and effectors which maintain constancy of the composition of body fluids. These include the hypothalamus and posterior pituitary with regard to water and the adrenal cortex, anterior pituitary, and perhaps the brain itself, with regard to some of the chief electrolytes. As we shall see, in later chapters, there is some overlap in that there is evidence for and against a posterior pituitary effect upon chloride and sodium excretion, and considerable data to support the concept that the adrenal cortex also influences water transfers.

### *C. Antidiuretic and Other Hormonal Substances as Regulators of Urine Volume*

Evidence is available indicating that there are areas or cells in the hypothalamus which are sensitive to the concentration of electrolytes and of water in the body. These are called osmoreceptors because they were first detected by Verney in experiments which proved them responsive to changes in the osmotic pressure of the perfusing fluids (3a, b). Subsequent studies have shown that there are other receptors which are sensitive to changes in the volume of body fluid even though the concentrations of the individual solutes are maintained quite constant (3c). The loci of the volume receptors have not been identified. However, one should think in terms of volume receptors as well as osmoreceptors. Clinical and experimental evi-



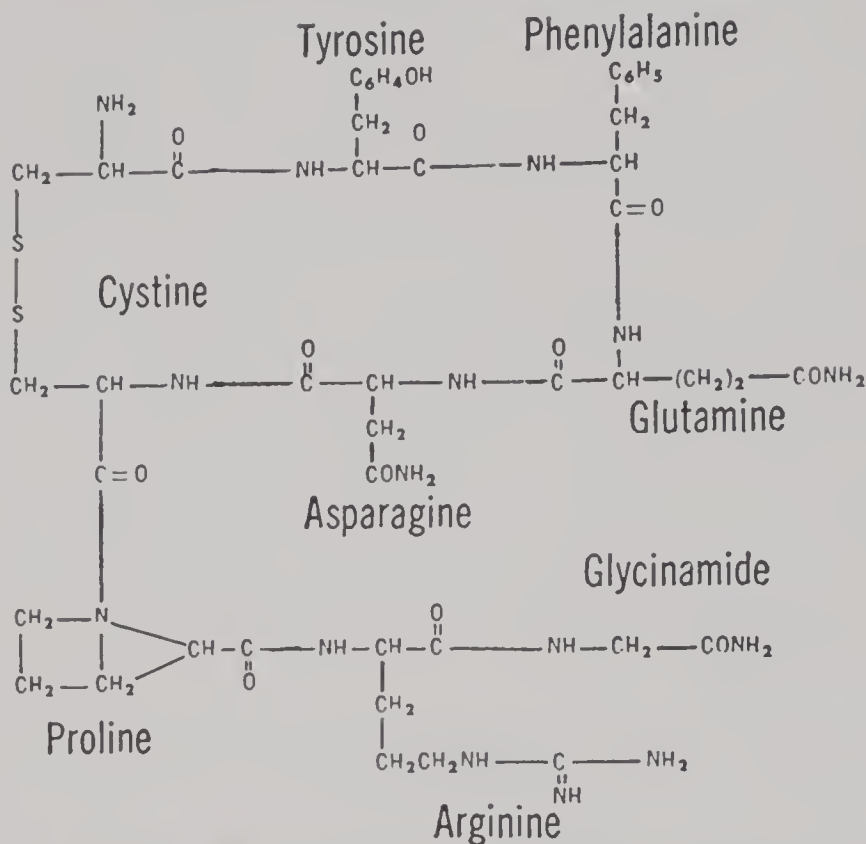


FIG. 5-1. PROPOSED AMINO-ACID LINKAGES IN ANTIDIURETIC SUBSTANCE ISOLATED FROM POSTERIOR PITUITARY BY duVIGNEAUD AND HIS GROUP (4b)

dence indicates that the osmoreceptors, their neural pathways, and the posterior pituitary are involved in the elaboration of an antidiuretic substance or substances. Structural formulae (fig. 5-1) consisting of linked amino acids based on analyses of beef and hog pituitary have been proposed by duVigneaud as representative of this agent or agents (4a, b).

These antidiuretic substances or hormones, often referred to as ADS or ADH, reach the renal tubules via the circulation and increase the reabsorption and hence diminish the excretion of water via the kidneys. The kidney tubules themselves possess the inherent capacity to reabsorb about 80 to 90 per cent of the daily volume of glomerular filtrate which amounts to some 180 liters (5). This statement is permissible in view of the fact that complete interruption of the mechanisms whereby antidiuretic substances reach the kidney tubules does not raise the daily urine volumes above eight or ten liters (6). ADH acts upon the remaining 10 to 15 per cent of the glomerular filtrate reducing its volume to one per cent or less by enhancing reabsorption. Fluctuations in the output of ADH in response to water loads effectively maintain body water within relatively fixed limits. This can be readily illustrated by describing the sequence of events which is induced in a normally hydrated healthy subject with intact electrolyte stores by: a) drinking pure water (7a), b) infusing a solution which resem-

bles extracellular fluid in composition (3c), or c) markedly restricting water intake (7b, c).

The absorption of several hundred cubic centimeters of ingested water at a time when body stores are intact will dilute body fluids. Such a decrease in osmotic pressure or tonicity of the body fluids will be registered in the osmoreceptors and less ADH is elaborated and the excess water as a consequence is eliminated via diuresis. A similar sequence of events will follow the administration of the artificial extracellular fluid, suggesting that there are receptors which also detect changes in the volume of the body fluids. On the other hand with water restriction the concentration of the body solutes rises and the volume of body water diminishes as a consequence of continuous losses of water via the lungs, skin, bowel, and kidney. An increased supply of ADH then becomes available and marked reabsorption of glomerular filtrate ensues. The volume of urine decreases and its specific gravity becomes high.

It was earlier indicated that some controversy existed concerning the effects of posterior pituitary preparations upon electrolyte excretion. The divergent opinions arise from the observation that in experimental situations some preparations produce an increase in the urinary output of chloride and of sodium while others do not (8a, b). This will be discussed in detail in chapter 19.

## II. Factors Regulating Body Sodium

It might be well at this point to comment upon the parallelism that exists between body sodium and chloride. Sodium is the predominant extracellular cation while chloride is the chief anion. Their concentrations are not however identical but rather approximate a ratio of 3:2. It is true that in a series of random urines obtained from healthy adults one can demonstrate a remarkable parallelism in the urinary excretion of sodium and of chloride. This is shown in figure 5-2. Also, it is true that procedures which deplete the extracellular electrolyte produce in general proportionate changes in these two ions. Similarly, dilution of body fluids will have comparable effects on the levels of these electrolytes. All of these facts might be taken as evidence in support of the thesis that chloride metabolism mirrors that of sodium. This is particularly attractive since measurements for chloride are far more generally available than those for sodium. Unfortunately in disease states the parallelism does not hold. We shall encounter this repeatedly in the disease processes and entities discussed in this book. This is in keeping with the experiences of others (9a). It is inadvisable therefore to accept knowledge of the amount of chloride present in urine or serum as equivalent to that of sodium. Facilities for the latter determination may not always be available but the limitations of chloride as a substitute should always be recognized.

*A. The Kidney, Adrenal Cortex, and Other Tissues in Absorption, Retention, and Excretion of Sodium*

Since the body is incapable of producing sodium, it naturally follows that endogenous sodium is always derived from intake. The content of NaCl in general diets is variable, ranging up to 10 to 15 grams each day (9b), but in ordinary circumstances even much smaller amounts prove adequate. The ingested sodium is completely or almost completely absorbed, since formed stools contain but little of this element (10a-c). The assimilated sodium enters the extracellular fluid where it can serve to maintain or to replenish body stores of this electrolyte, but it should be kept in mind that sodium is present to a varying degree in cells and that large and relatively labile stores of sodium exist in bone (11a, b). The relative constancy of serum sodium concentrations described in the preceding chapter points to the existence of homeostatic mechanisms. One of the most important of these is the ability of the body to vary the renal output of this ion.

As in the case of water the kidneys possess an inherent capacity to re-absorb the bulk of the filtered sodium (5). Steroids of the adrenal cortex

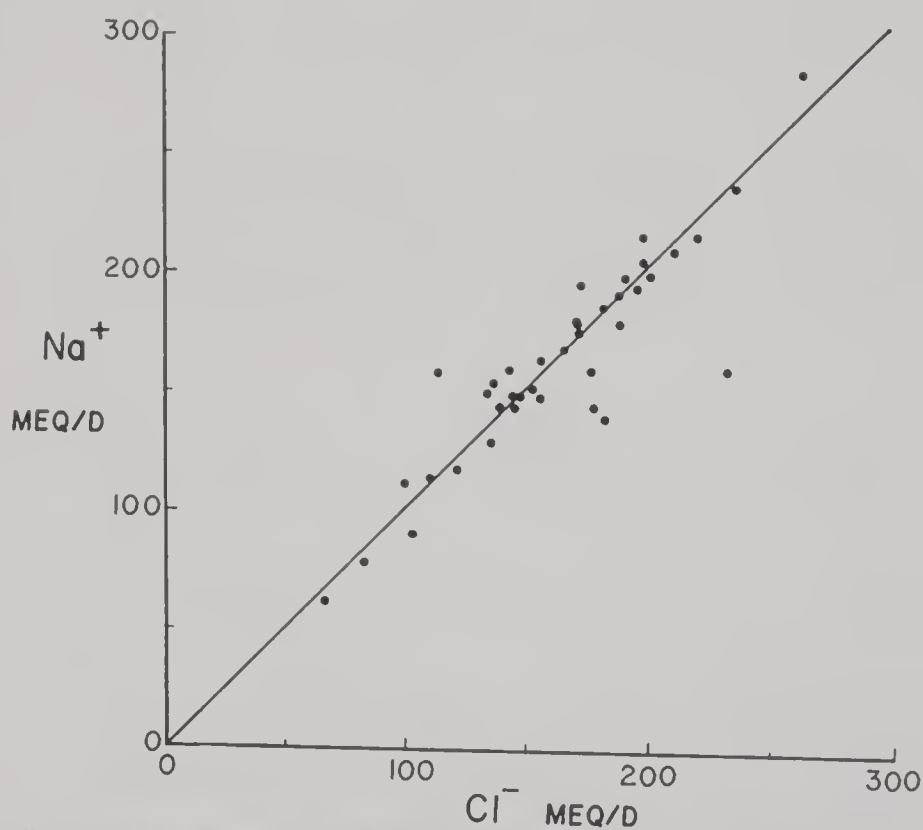


FIG. 5-2. PARALLELISM OF URINARY SODIUM AND CHLORIDE EXCRETION IN HEALTH

In this group of healthy young children analysis of 24-hour urines collected sporadically indicates a pronounced parallelism of urinary sodium and chloride output. Unfortunately this does not occur with the same frequency in disease states and hence chloride output cannot be used as an index of sodium excretion. (Danowski *et al.*, unpublished data.)



augment this ability and variations in the amount of these compounds reaching the renal tubules determine in great measure the final reabsorption or excretion of this ion. The contribution of the adrenal cortex in this regard and the basis for the statement relevant to the inherent sodium-reabsorbing capacity of the kidney can both be illustrated by referring to the changes induced by adrenocortical insufficiency. In this condition, to be discussed in greater detail in chapter 18, the reabsorption of sodium is inadequate. If sodium is not provided in sufficient amounts to such patients, deficits of this ion develop. The important point to make however is that such deficits do not develop in a matter of hours, which would be true if the reabsorption of sodium were 100 per cent dependent on adrenocortical steroids.

The recent studies of Reichstein suggest that such reabsorption may well be mediated through a particular steroid isolated from the amorphous fraction which has been named aldosterone or electrocortin and for which he has suggested a chemical formula (fig. 5-3). Some of its effects appear to be similar to those of other known steroids save that they are elicited with much smaller amounts of electrocortin. This agent appears to be for example some 25 to 50 times as active as desoxycorticosterone, a mineralo-steroid, in facilitating sodium reabsorption; desoxycorticosterone is in turn some 30 to 50 fold as effective as Compound E or cortisone in this regard (12a-e).

Some simple and interesting animal experiments clearly illustrate the participation of the adrenal cortex in sodium reabsorption or excretion. The maintenance of rats on a sodium-free regimen results in marked hypertrophy of the adrenal cortices with evidences of increased secretory

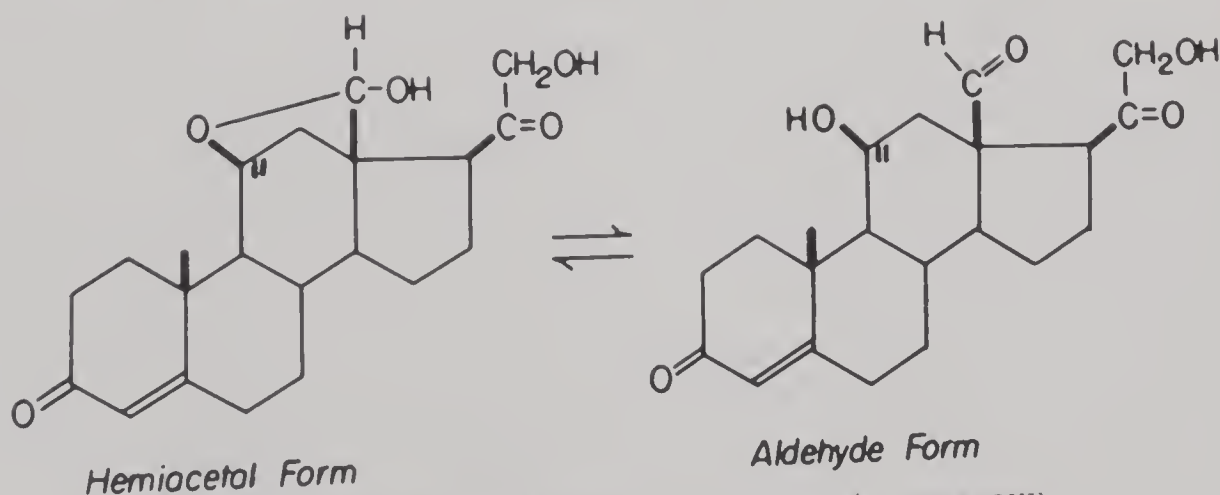


FIG. 5-3. FORMULA OF ELECTROCORTIN OR ALDOSTERONE

Reichstein and co-workers propose that this newly isolated steroid with potent mineral effects exists in equilibrium as an aldehyde and a hemiacetal. It is to be noted that an oxygen is present on the 11 position in the third ring. In this respect it resembles oxysteroids such as cortisone and hydrocortisone and differs from DOCA or desoxycorticosterone (12a, b).

activity, while extra loads of sodium result in a decrease in the size of the adrenal cortex with diminished activity (13a-c). These morphologic changes reflect the response of the adrenal cortex to the need to conserve filtered sodium as completely as possible. This is achieved by virtue of the kidneys inherent capacity together with the supererogatory influence of the salt-retaining steroids. Within a matter of days the urine becomes virtually sodium-free. This adaptation is illustrated in figure 5-4 based on studies in rats (13d). If extrarenal sodium losses do not occur, such a subject can continue indefinitely recirculating his own sodium stores without need for

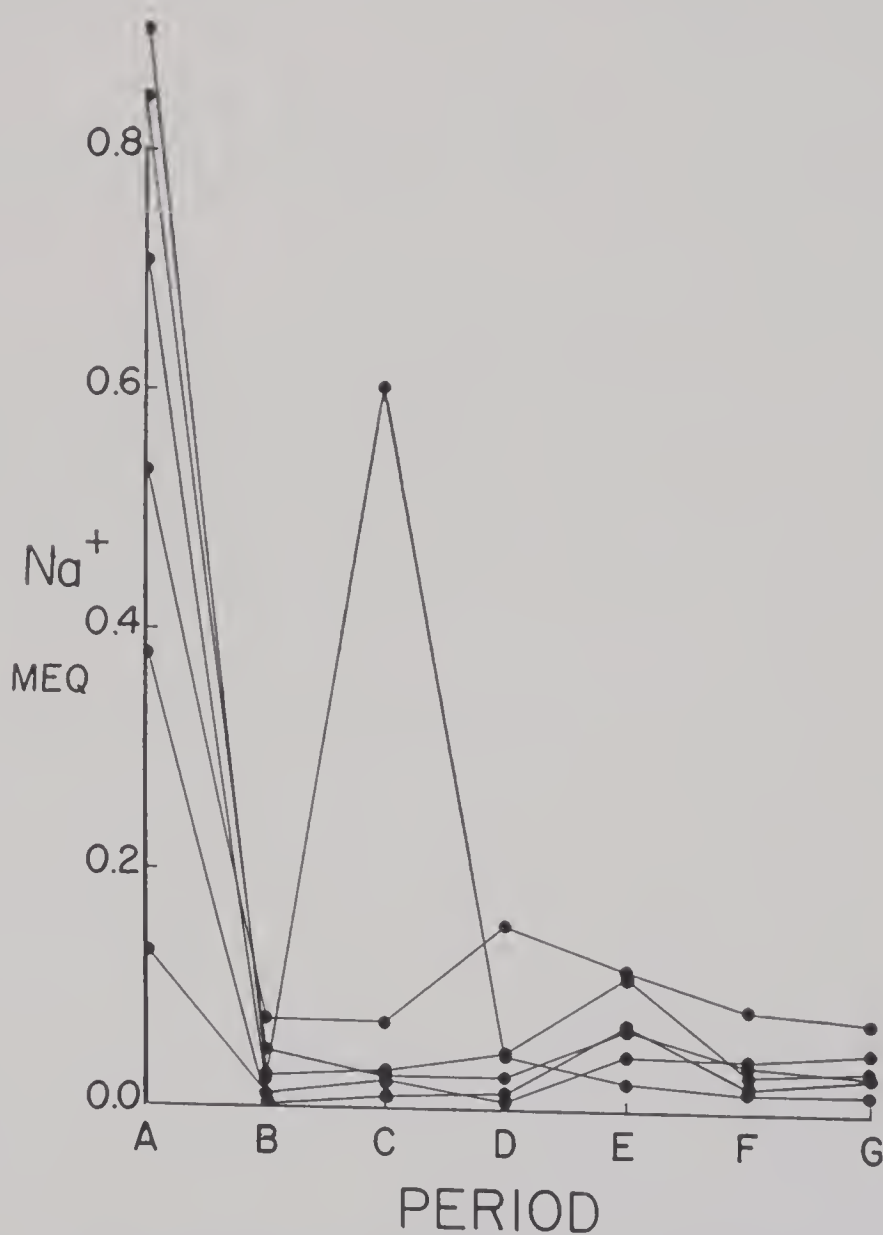


FIG. 5-4. RENAL RESPONSE TO SODIUM DEPRIVATION

Each of these rats was maintained on a diet free of all electrolytes but chloride. The absence of an intake of sodium promptly evoked a sodium conservation response with the elaboration of a urine free of this electrolyte. This became maximal within 3 to 6 days. (Danowski *et al.*, unpublished data.)

replenishment. On the other hand the "atrophic" adrenal cortex which develops with increased sodium loading reflects the diminished need for re-absorption of this ion.

Incidentally it should be indicated that these steroids can be shown to influence the output of sodium via the sweat glands and via the gastrointestinal tract in the same direction as their renal effects. The first of these is directly demonstrable by collecting sweat from patients with normal, increased, or decreased function of the adrenal cortex (14a-d). The gastrointestinal effect is detectable only by the use of exchange resins (see chapter 9) which augment the sodium content of feces. In patients with adrenocortical insufficiency these resins remove amounts of sodium which are several fold higher than those otherwise achieved (15a). Other indirect evidence of a similar type has been offered based on observations of patients with body fluid excesses in whom evidences of concomitant hyperadrenocorticism were present (15b, c). In such subjects the resins were thought to be less effective than usual.

Though the discussion up to this point has emphasized the role of the adrenal cortex this must not be taken to mean that this is a self-sufficient organ and that the adjustments that have been cited are confined to it. As a matter of fact, to the as yet incompletely defined role of anterior pituitary adrenocorticotrophin in sodium metabolism must be added the further question of the relationship of higher neurologic centers. Clinical evidence is available indicating that disturbances of sodium metabolism may accompany brain lesions (16a-d). This last point is discussed in greater detail in chapter 17.

### III. Factors Operative in the Maintenance of Body Potassium

#### *A. Fate of Ingested Potassium*

Figure 5-5 summarizes the sites of body potassium in health. As in the case of sodium the potassium inside and outside of cells is ultimately derived from dietary constituents which provide some four to eight grains per day from plant and animal cells (9b). The stools contain more potassium than sodium (10a-c). This suggests a less complete absorption of potassium as compared to sodium, but it may also represent a relatively greater secretion of potassium. Though the bacteria of feces are cells and therefore contain potassium, they cannot account for the greater fecal output of this ion. The fact remains that in terms of net balance the gastrointestinal loss of potassium is greater than the output of sodium via this route.

The absorbed potassium enters the extracellular fluid. It may then become incorporated into cells where its concentration is usually 15 to 20 times that outside of cells, remain in the extracellular compartment, or be excreted via the urine, gastrointestinal tract, or the skin (17a-c).



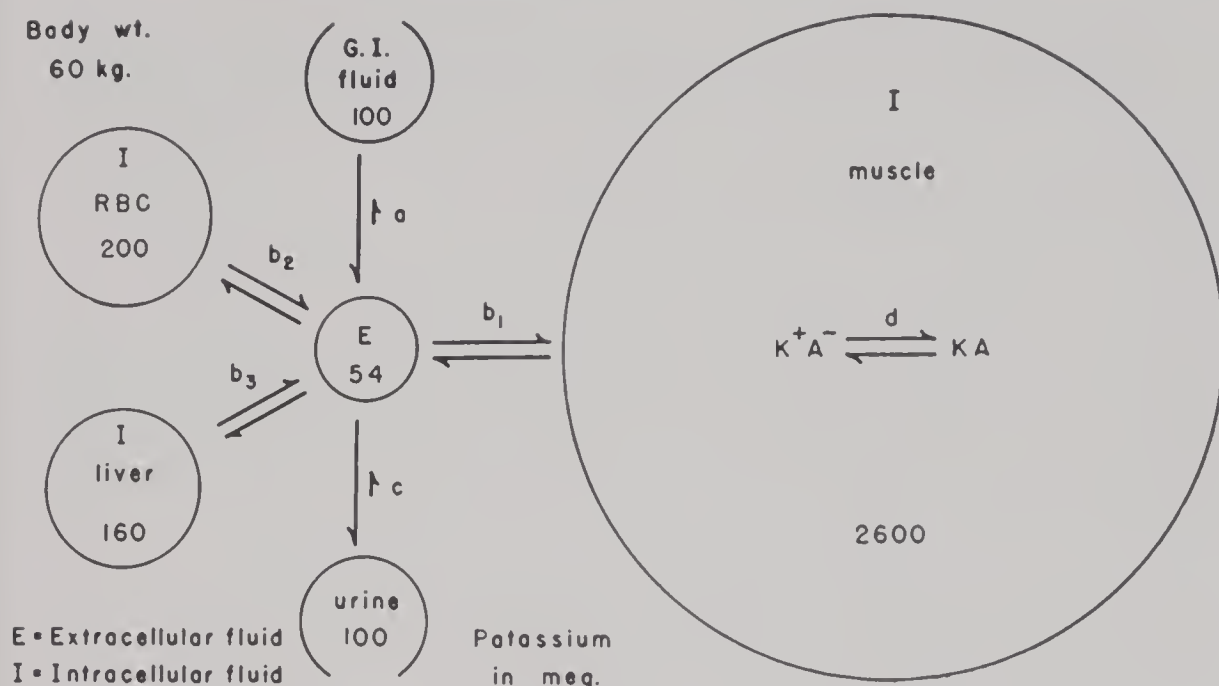


FIG. 5-5. DIAGRAM OF THE PRINCIPAL DEPOTS AND TRANSFERS OF POTASSIUM IN THE BODY

Areas of circles are proportional to the total amount of potassium in each extracellular and intracellular depot of a 60-kg. subject. Arrows represent the main transfers of the ion; the intake from the gastrointestinal tract ( $a$ ), the output through the kidneys ( $c$ ), and the exchanges between cellular depots and extracellular fluid ( $b$ ). Changes in the degree of dissociation or osmotic activity within the cell are indicated ( $d$ ).

### B. Transfers of Potassium between Cells and Extracellular Fluid

The unequal distribution of potassium between cells and the surrounding fluid, referred to earlier, exists only in the living organism. With death, potassium pours out of the cells until its concentration is equal in the water on both sides of the cell membrane. Similar losses of cell potassium can be observed with anoxia. As described in figure 3-2, in chapter 3, in the isolated blood cell system interruption of carbohydrate metabolism by refrigeration, exhaustion of glucose supplies, or exposure to inhibitors of glycolysis such as fluoride also produces losses of cell potassium.

Insofar as the entry of potassium into cells is concerned it should first be pointed out that normal growth or repair inevitably involves the incorporation of this element within cells, since it is characteristically present there and in relatively fixed proportions. Also, the formation of glycogen in liver or the reformation of muscle glycogen also must involve cellular segregation of potassium, since glycogen is laid down with more or less fixed proportions of electrolytes and with potassium in particular. Glycolysis in tissues or in blood cells is accompanied by transfers of potassium (18a, b). Finally, it is recognized that a net gain of cell potassium can occur

even in the absence of any of these processes. This is readily demonstrable by administering a known amount of a stable or radioactive potassium salt and noting that, before the final renal adjustments are made, the potassium ion distributes itself in a volume of body fluid which exceeds the extracellular space in magnitude (17a-c).

### *C. Role of the Kidney in the Excretion and Retention of Potassium*

The extracellular levels of potassium represent the net balance, in a sense, of the potassium that is ingested, that portion incorporated into cells, and that portion which is excreted. The relative constancy of the serum values of this electrolyte points to the presence of regulatory mechanisms. Again, as with water and sodium, the kidneys and humoral factors occupy key positions in effecting the excretion of this electrolyte. At present it is uncertain what proportion of filtered potassium, if any, is actually excreted in urine as a consequence of incomplete tubular reabsorption. It is unquestioned that tubular secretion or excretion of potassium does occur since in certain instances glomerular filtration cannot possibly account for all of the potassium which appears in urine (19a-e). Hence it seems valid to take the position at this time that the relative magnitude of the contributions of glomerular filtration and tubular activity to potassium excretion are incompletely defined. The matter however will be discussed in further detail in chapter 10 in defining the role of the kidney in anion-cation balances.

The urinary excretion of potassium is also under hormonal influence. The adrenocortical type steroids cited in discussing sodium, i.e., corticosteroids, desoxycorticosterone, and Compound E, as well as ACTH all facilitate the excretion of potassium. Hence with potassium loading the adrenal cortices hypertrophy while with deprivation they decrease below normal in size (13a-c). It appears probable however that, under clinical circumstances the renal conservation of potassium when the intake is reduced to zero is not as prompt nor as precise as is the case with sodium under similar conditions (20a-g). Recent studies in rats and in humans have indicated however that in healthy subjects not undergoing stress a potassium conservation response can be induced (13d, 20b). This is illustrated in figure 5-6. This adaptation appears to be less effective or is lost in ill patients, perhaps for the very reason that sodium conservation is so complete, i.e., either because adrenocortical discharge has opposite effects on sodium and potassium output, or because the reabsorption of at least some of the sodium involves an exchange for potassium. Figure 5-7 shows that potassium deprivation in human volunteers (20c) undergoing starvation and dehydration was not accompanied by complete conservation of potassium, presumably because this regimen produced stress.

#### IV. Regulation of Body Stores and Concentrations of Chloride, Calcium, Phosphorus, Bicarbonate and Other Electrolytes

##### A. Chloride

Chloride in general terms is currently considered to be subject to the same influences which act upon sodium. Certainly this is supported by the frequency with which changes in the serum concentration of one of these ions are reflected by roughly comparable changes in the other. This type of relationship in urine has been illustrated in figure 5-2. Such excellent agreement between the urinary output of sodium and chloride is not present however in all disease states and suggests that separate influences act upon

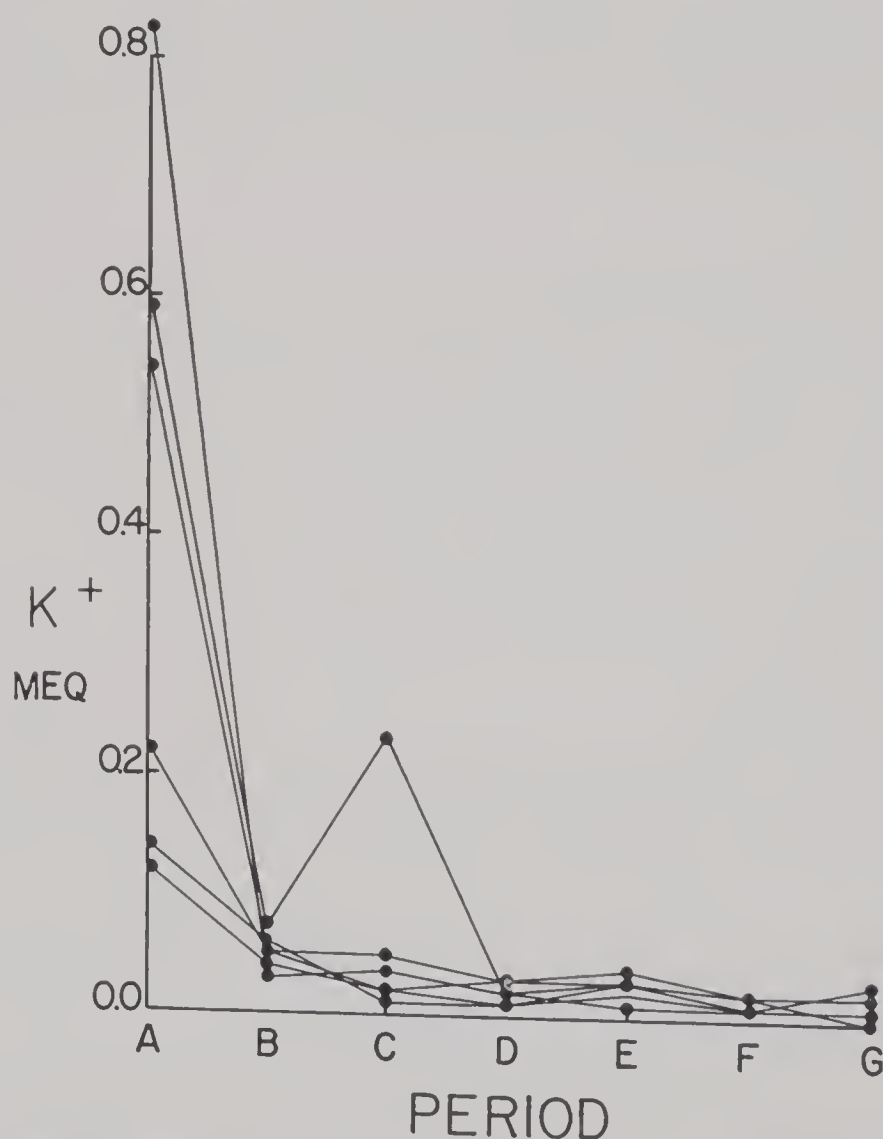


FIG. 5-6. DECREASED URINARY EXCRETION OF POTASSIUM FOLLOWING WITHDRAWAL OF DIETARY POTASSIUM

After 2 periods of 3 days each a prompt and definite renal conservation of potassium became maximal in each of these rats as the intake of this ion was sharply reduced to zero. (Danowski *et al.*, unpublished data.)



these ions or that their responses to the same stimuli are different. Thus, adrenocortical steroids act, if the studies of Pullman (21a) with desoxycorticosterone can be taken as a prototype, upon sodium only and hence the accompanying changes in chloride are secondary. On the other hand, as indicated in chapters 9 and 13, mercurial diuretics influence sodium excretion secondary to increased excretion of chloride. Finally, though information is available concerning the position of chloride in the hierarchy of anions competing for reabsorption (21b), the definitive statements concerning the renal tubular exchanges of chloride cannot as yet be made.

### B. Calcium and Phosphorus

The two most clearly defined regulators of calcium and phosphorus metabolism known to date are the vitamin D hormones and the parathyroid glands. The detailed studies of Albright and his colleagues and contemporaries indicate that vitamin D has two primary effects: it increases the ab-

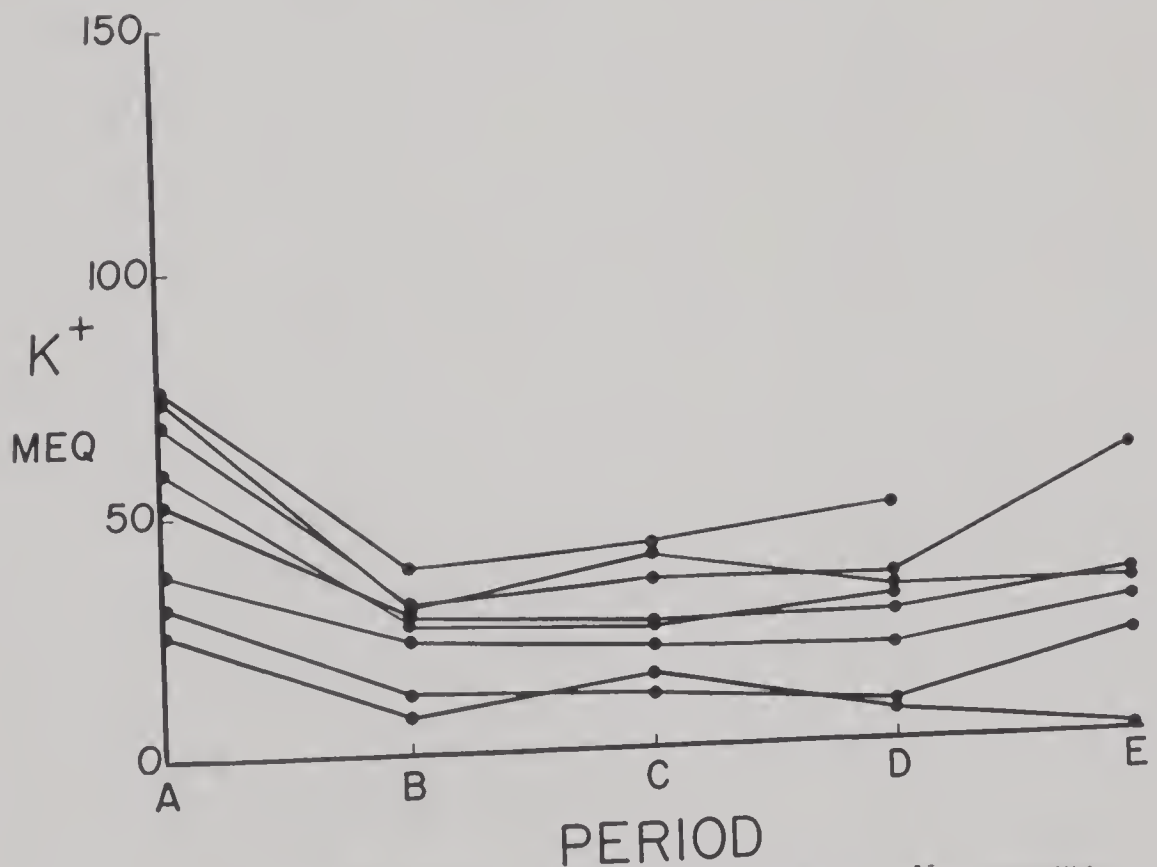


FIG. 5-7. RENAL EXCRETION OF POTASSIUM IN HUMAN VOLUNTEERS UNDERGOING TOTAL DEPRIVATION OF FOOD AND WATER

The withdrawal of dietary potassium decreased somewhat the urinary output of this ion, but excretion continued. This presumably reflects the physiologic effects of the dehydration, starvation, and stress to which these men were subjected, since in the rats (fig. 5-6) distinct potassium conservation appeared when this electrolyte was eliminated from an otherwise normal regimen. (From Winkler *et al* (20c).)

sorption of ingested calcium and raises the urinary excretion of inorganic phosphorus from the body. Dihydrotachysterol (or A.T. 10) differs from vitamin D in that it exerts less of an effect upon the gastrointestinal tract and produces a greater increase in urinary phosphorus excretion (22a-d). Parathormone on the other hand acts predominately on the kidneys and again raises the urinary output of inorganic phosphorus and has much less of an effect on the composition of feces (23a-d). It does however have a direct action on bone causing dissolution (23d). However, as in the case of the adrenal cortex and the antidiuretic substances with respect to electrolyte and water metabolism, vitamin D and parathormone are surely not the sole regulators of calcium and phosphorus metabolism. Thus it will be seen in subsequent sections of this text that in malnutrition, in renal and gastrointestinal disease states, in patients with inadequate or excessive estrogen supplies, the stores and levels of calcium and phosphorus are indirectly or directly modified.

### *C. Magnesium*

Information concerning magnesium is quite scanty because of difficulties with the available analytic techniques and hence the fundamental aspects of the regulation of magnesium metabolism have not been defined. It is known however that deficiency in rats may cause convulsions, that excesses produce vasomotor depression and respiratory failure, that in myxedema the binding to protein decreases to zero while it rises to approximately 50 per cent in hyperthyroidism, and that in diabetic coma or in renal failure rises above the usual range of normal do occur. These changes are described in greater detail and with bibliographic support in chapter 23.

### *D. Bicarbonate*

Of the remaining quantitatively important anions in the Gamble diagram bicarbonate metabolism is sufficiently complicated to warrant coverage in a separate section (chapters 10 and 11).

**SUMMARY:** The relative constancy of the body weight, body water, sodium, potassium and other electrolytes despite large fluctuations in intake point to the existence of regulating mechanisms which maintain the volume, composition, and distribution of body fluids. In such regulation the kidneys and the circulation play key rôles. The antidiuretic hormone of the posterior pituitary operates to maintain concentration of body water, and the adrenal cortices regulate the output of the chief electrolytes. Other mechanisms undoubtedly exist for the control of the water, sodium, potassium, and other solutes in body fluid.

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## *Chapter 6*

### **COMMON DENOMINATORS IN DISEASE STATES LEADING TO DEFICITS OF BODY CONSTITUENTS**

A working knowledge of the material presented in the preceding chapters, i.e., of mechanisms operative in the maintenance of body water, anions, and cations, is essential for discussions of the common denominators which result in deficits of water and electrolytes in disease states. These include starvation, dehydration, vomiting, diarrhea, sweating, renal function and dysfunction.

#### **I. Starvation with Water Available as Desired**

Loss of appetite is a frequent accompaniment of many diseases. Interruption of all intake but water under these or similar circumstances is soon followed by a decrease in or absence of stool output, and a loss of body weight. The latter occurs despite the fact that sufficient water is available. Such weight loss is due primarily to a loss of body solids, i.e., carbohydrate, protein, and fat, sacrificed to provide energy for metabolic needs, though some water is lost as well. The depolymerization of liver glycogen releases potassium and smaller amounts of other cations. However in its net effect this is a small contribution both in calories and in electrolytes since the body stores of liver glycogen are limited and soon consumed. In protracted starvation the body relies chiefly upon fat and tissue protein. Combustion of the latter foodstuff releases a more or less predictable amount of cell potassium. In addition, nitrogenous products, chiefly urea, accrue from the degradation of the protein molecule, and acetone bodies accumulate when fatty acids are mobilized in excess of the capacities of tissues and organs to catabolize or to excrete these products (1a-c).

The kidney under conditions of restricted or absent intake of minerals and calories endeavors to conserve certain body constituents. Thus within

a matter of several days the urinary output of sodium declines, as discussed in chapter 5 and illustrated in figure 5-4, and may reach levels indistinguishable from zero. Similarly the sodium content of sweat decreases. Urine potassium excretion on the other hand continues to be quantitatively significant, and in many patients produces notable deficits of this electrolyte. Hence the net effect of acute food deprivation is a destruction of body tissues and a loss to a variable degree of some of the body potassium in urine (1d-j).

In prolonged starvation, as in that seen in war prisoners, it has been noted that the extracellular fluid becomes unduly expanded, for reasons which have not been satisfactorily defined. The serum albumin levels are lowered as are the concentrations of cholesterol (1k-m). Other blood solutes are well-maintained in these subjects. On the other hand when chronic potassium deficits occur in experimental animals hypokalemia, hyponatremia and alkalosis may develop. In animals deprived of potassium muscle potassium is decreased while sodium rises (1n-p). The mechanisms operative in this last group of changes are discussed in chapters 7 and 10.

## II. Dehydration

### A. Clinical and Physiologic Aspects

Deficits of body water occur in their least complicated form in patients or subjects who for any reason do not receive and retain an adequate daily supply of water, e.g., in neglected or unconscious adults or children, in patients with obstructive lesions of the upper gastrointestinal tract, in mentally disturbed individuals who refuse fluids, and in persons deprived of fresh water at sea or in the desert. For the moment, we shall ignore the starvation which is frequently also present, with a promise to return to it following the discussion of dehydration *per se*.

The water deficits which result from inadequate water supplies are attributable primarily to the inability of the body to reduce greatly the insensible loss of water through the skin and lungs. It has already been indicated in chapter 5 that this loss is approximately one liter each day. In addition body water is lost via the kidneys, since urine formation continues. This decrease in body water evokes an increased output of antidiuretic substances and, as indicated in chapter 5, the urine volume declines to the irreducible minimum, some 250 to 350 cc. in each 24-hour period in adults.

This cutback in the loss of water via the kidney of course will not prevent progressive dehydration. This is true not only because urine formation does continue, even though at a reduced rate, but also because the extrarenal losses are only slightly decreased. Thus insofar as the insensible output of water is concerned, the rise in osmotic pressure in body fluids as a result of



dehydration and the diminution in the vapor pressure can be expected to effect only minor decreases in the losses through evaporation.

Thirst is the cardinal symptom of dehydration. It is closely correlated with antidiuresis, hypertonicity of body fluids, and intracellular water deficit. This symptom in any sick patient therefore merits careful consideration.

### *B. Transfers of Water from Cells Mitigate Extracellular Dehydration*

Since these losses of body water occur through surfaces adjacent to the extracellular fluid, it is evident that the volume of this compartment will decline. However, a number of mechanisms can result in internal transfers of water from cells to surrounding fluid and thereby reduce the degree of extracellular dehydration (2a-f). The first of these is related to the osmotic sequel of removing water from the extracellular fluid without decreasing the number of solutes present therein. This consists of a transfer of water from the cellular phase until the differential osmotic pressure between these two phases is cancelled. This is illustrated in figure 6-1. It should be apparent however that, even though the dehydration (incurred initially through extracellular media) is thereby distributed through the two major compart-

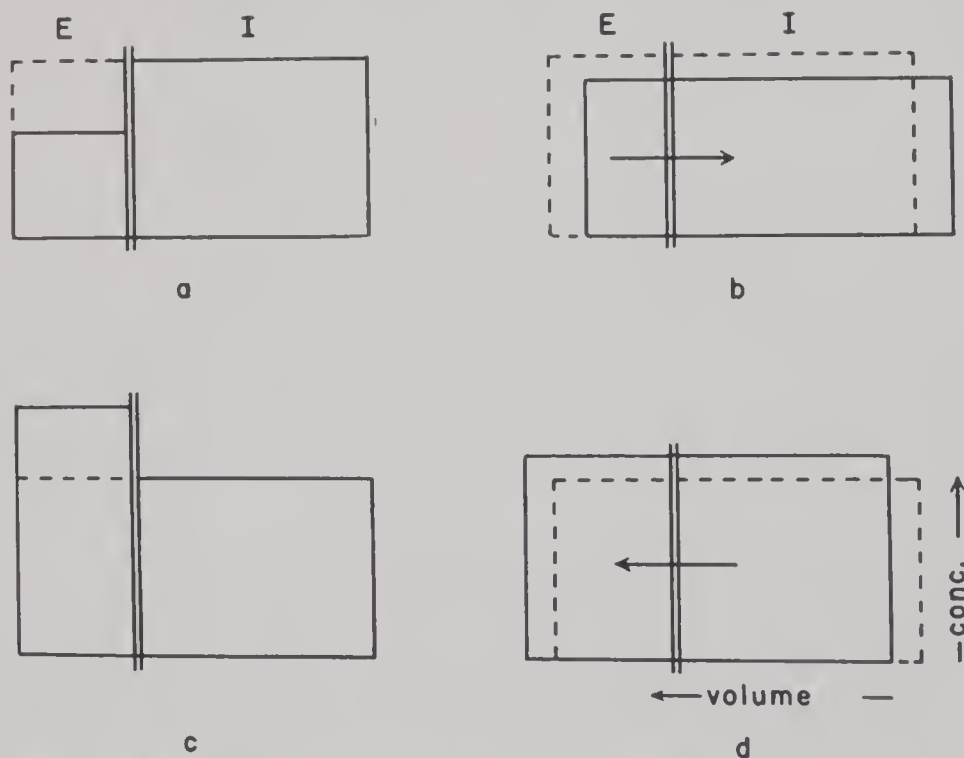


FIG. 6-1. OSMOTIC TRANSFERS OF WATER BETWEEN EXTRACELLULAR AND INTRACELLULAR COMPARTMENTS IN RESPONSE TO CHANGES IN THE EXTRACELLULAR CONCENTRATION OF ELECTROLYTE; ILLUSTRATED BY MEANS OF DARROW-YANNET DIAGRAMS

The reduction of concentration in E (a) causes transfer of water from E to I or cellular overhydration (b). Elevation of concentration in E (c) causes transfer of water from I to E or cellular dehydration (d).

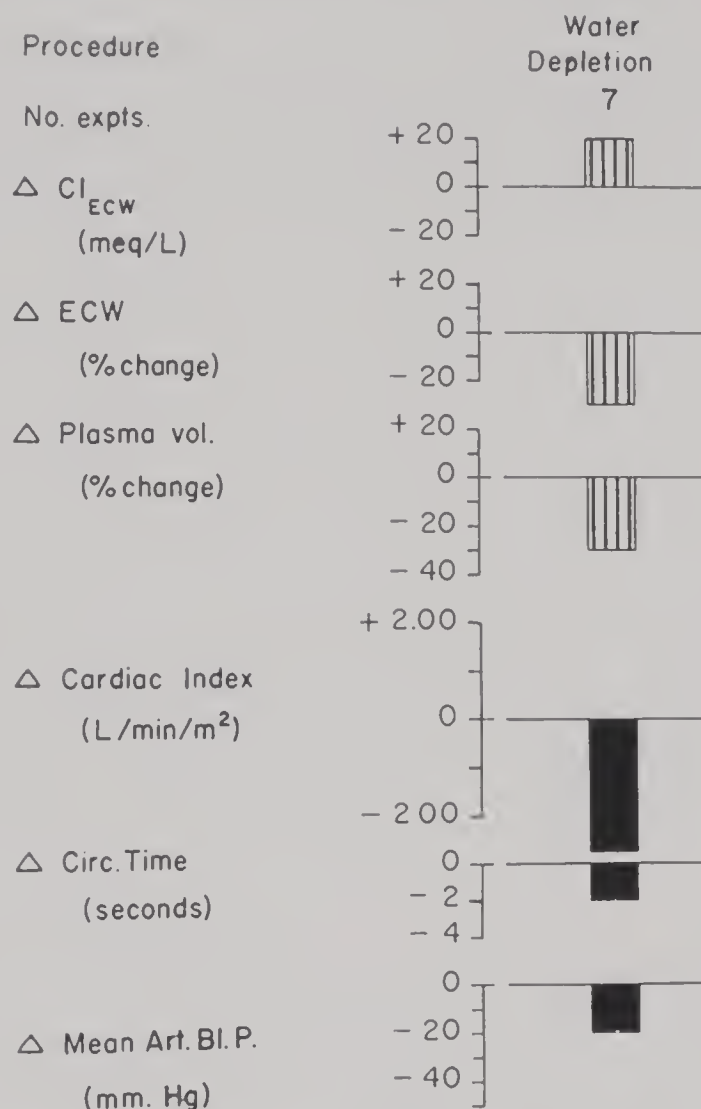


FIG. 6-2. WATER DEPLETION IN DOGS

The end result of dehydration produced by urea diuresis includes hyperelectrolyt-emia as reflected in the increased chloride levels and a proportionate depletion of extracellular and plasma volumes. Though not shown above, an equivalent cellular depletion was present since water freely crosses cell membranes. (From Elkinton *et al* (2d).)

ments of body water, it is nonetheless still present. This is seen in the experiments summarized in figure 6-2 (see also Fig. 2-6).

As dehydration and hypertonicity progress, another process is initiated which releases a further modicum of cell water. This is illustrated in figure 6-3 under the term "dehydration reaction"; it is a renal response characterized by the excretion of potassium at the expense of sodium (2a, c, f) and presumably is the result of the tubular secretion of the former cation. The transfer of this electrolyte not only lowers the osmotically active components in cells but also simultaneously raises those in the interstitial fluid and plasma. Again the osmotic pressure differentials between the two phases are prevented by a net gain of water by the external compartment.

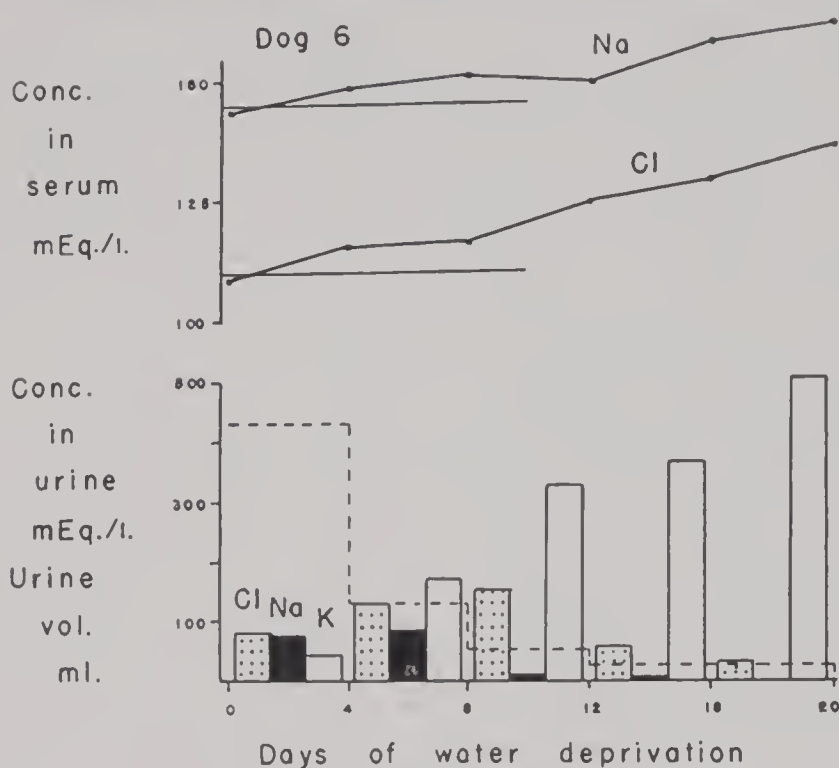


FIG. 6-3. THE "DEHYDRATION REACTION"

During water deprivation in the dog the potassium concentration in urine rose while that of sodium and chloride fell, despite the progressive rise in concentration of these latter ions in the serum. The volume of urine (dashed line) fell as water was conserved. (From the data of Elkinton and Taffel (2a).)

A third adjustment to dehydration and hypertonicity, also related to osmotic effects, can be cited. Its existence is based on deduction from transfer studies which indicate that the total osmotically active base of cells can vary in amount (3a). Furthermore, such increases or decreases can occur without movement of cations and therefore may be akin to complexing or sequestering reactions of the type seen with chelating agents (3b). Such a cancellation of the osmotic effects of cations in solution in the cells of dehydrated patients can be expected in turn to release water from cells as a result of a simultaneous absolute decrease in the hypertonicity.

It should be emphasized that in this type of dehydration we are dealing primarily with deficits of body water. The body electrolyte stores remain relatively intact, even though some urinary excretion of anions and cations may continue at a reduced rate and potassium is known to leave the cells.

### C. Effects of Starvation and Dehydration

The superimposition of starvation upon dehydration modifies the rate at which the latter occurs as well as its degree, depending upon whether it is complete or partial and upon the food given. In total starvation the decreased energy turnover reduces the water of oxidation made available



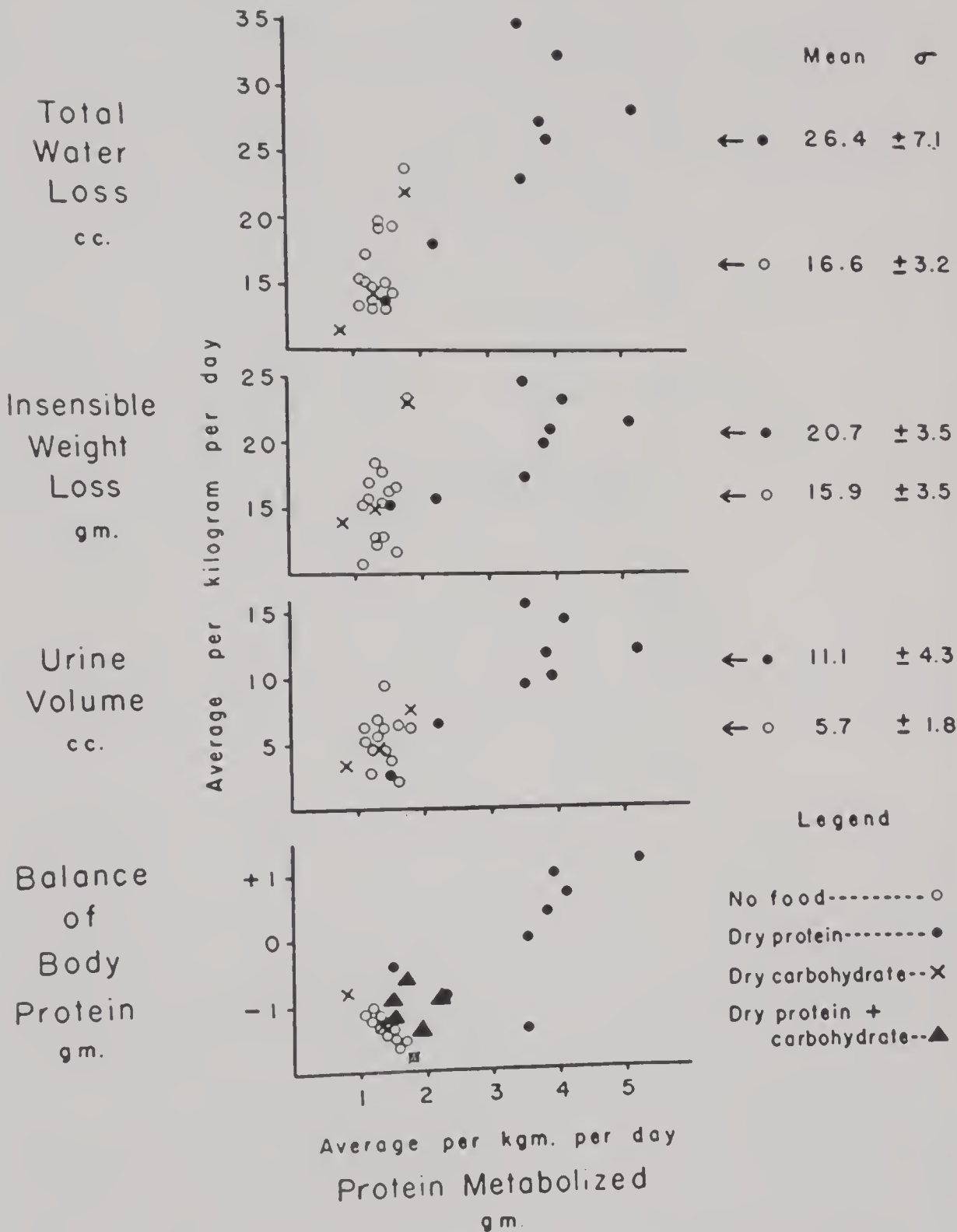


FIG. 6-4. EFFECTS OF INTAKE ON BALANCES OF WATER AND PROTEIN IN DOGS DEPRIVED OF WATER

Protein metabolized is chartered against total water loss, insensible weight loss, urine volume, and balance of body protein, expressed as averages per kg. per day. The animals fed dry protein plus carbohydrate are only plotted in the lowest figure since they overlie the control groups.

It is evident that dry protein may spare body protein but accelerates dehydration. In dogs carbohydrate ingestion diminished dehydration chiefly by sparing body protein. (From Danowski *et al* (3c).)

through the combustion of foodstuffs or body tissues. On the other hand, in some measure this is counterbalanced by the decreased production of calories which decreases the need for insensible perspiration for the dissipation of heat. Furthermore, since cessation of food intake is usually followed by marked constipation or by passage of only small desiccated stools, the loss of water which normally occurs in feces is essentially eliminated. Finally, the load of solute presented to the kidney for excretion, consisting chiefly of urea and of electrolytes, will also be decreased in starvation.

The effects of partial starvation upon dehydration will depend upon the foodstuff which is provided. Thus a high intake of carbohydrate without fat or protein will diminish both the breakdown of endogenous protein and the formation of ketone bodies. This decreases the urinary solute load and thereby permits maximal reduction in urine volumes. On the other hand, ingestion of fat only will increase ketone body formation but may serve to minimize negative balances of cell nitrogen. Finally, a high protein ration will inevitably raise the urea output, increase the urine volumes, and accelerate dehydration (3c-e). This can be readily seen in figure 6-4 which illustrates experimental studies concerning this point.

### III. Vomiting

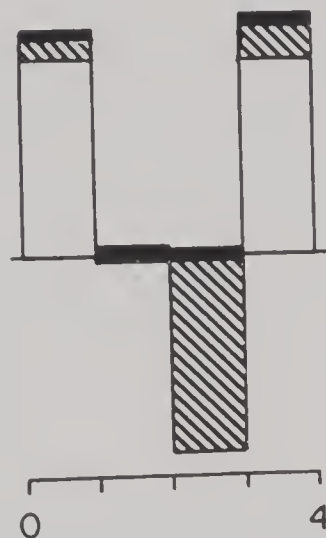
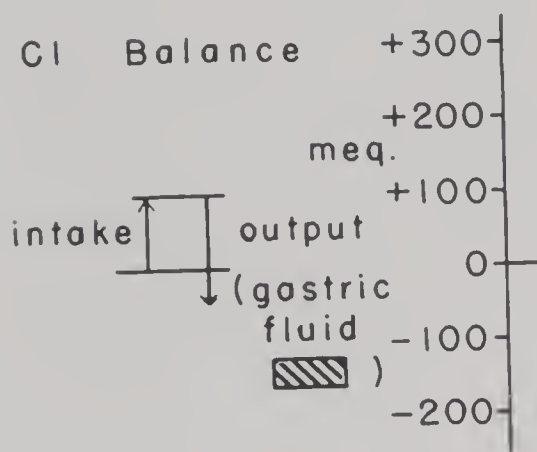
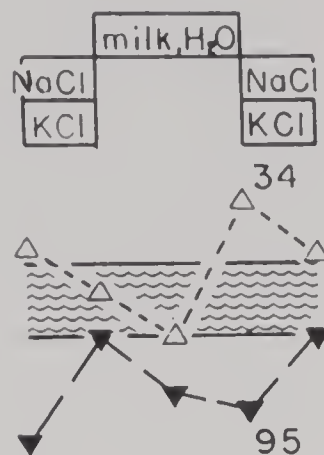
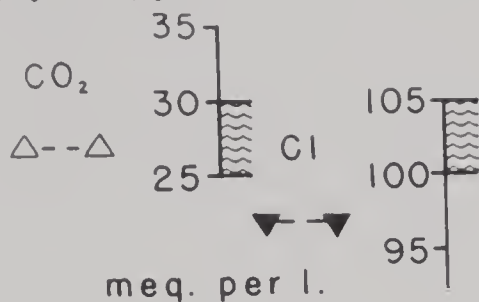
Vomiting is accompanied by all of the changes which have been described in the section on dehydration and starvation. This is understandable since vomiting interferes with the intake of fluids and of foods. Such patients also develop negative balances of body constituents as a result of losses in the vomitus. Gastric secretion contains considerable amounts of sodium and of potassium in addition to its high content of either hydrochloric acid or chloride (4a-e). The losses of the chloride ion understandably result in hypochloremia and a metabolic alkalosis (fig. 6-5). The latter stems from the fact that the losses of extracellular chloride in vomitus are greater than the losses of sodium. In keeping with the principles enunciated in chapters 10 and 11 carbon dioxide is then retained and plasma bicarbonate increases to make up the discrepancy between the losses of anions and cations. In the uncompensated phase this increase in bicarbonate will be accompanied by a rise in pH. The magnitude of the metabolic alkalosis and the pH change may be somewhat diminished by decreases in the extracellular fluid concentrations of sodium and of potassium.

Irrespective of whether or not hyponatremia and hypokalemia appear, vomiting patients do develop deficits of these cations. As a matter of fact such losses may be present in the face of normal or elevated concentrations of these electrolytes (4f-i). This is illustrated in figure 6-6. The seeming disparity between high concentrations and decreased body stores is readily resolved by the recollection of the fact that concentrations are influenced by water balances as well as electrolyte balances. Hence, if water and elec-

Patient H.H. Post-op. pyloric ileus

Therapy

Serum conc.



Day of study

Interpretation of serum concentrations

Normal Patient meq. per l.

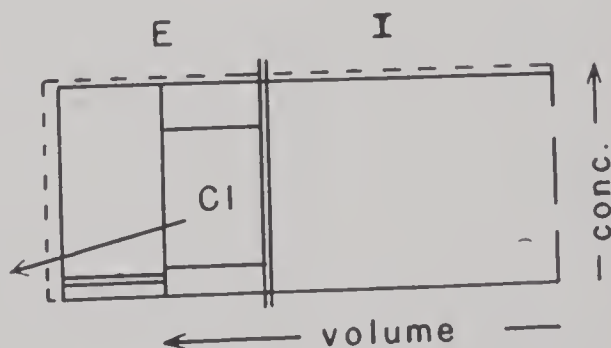
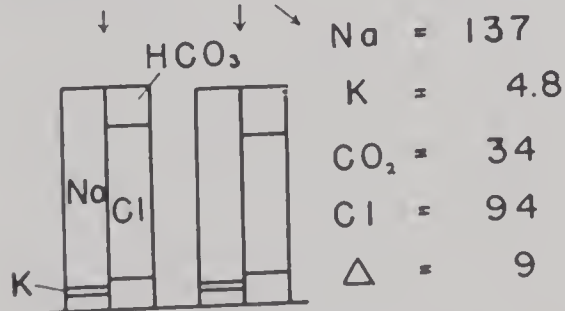


FIG. 6.5. CHLORIDE DEPLETION AND HYPOCHLOREMIC METABOLIC ALKALOSIS DUE TO LOSS OF GASTRIC FLUID

H. H. was a 67-year-old white male recovering from a cholecystectomy complicated by paralytic ileus. On day 3 of period shown, ileus returned and large amounts of gastric fluid were again lost; replacement therapy was reinstituted on day 4 with restoration of chloride balance.

Interpretation of serum concentration at end of day 3. *Body fluid pattern:* Deficit of chloride replaced by bicarbonate excess in extracellular fluid, without change in sodium concentration and only slight decrease in extracellular volume. No significant change in intracellular sodium or potassium occurred during the development of this hypochloremic alkalosis (see also fig. 11-9).

*Physiologic mechanism:* Loss of gastric fluid containing chloride greatly in excess of sodium ( $\text{Cl} = 132 \text{ mEq./l.}$   $\text{Na} = 6 \text{ mEq./l.}$ ). (From Squires and Elkinton (4c).)



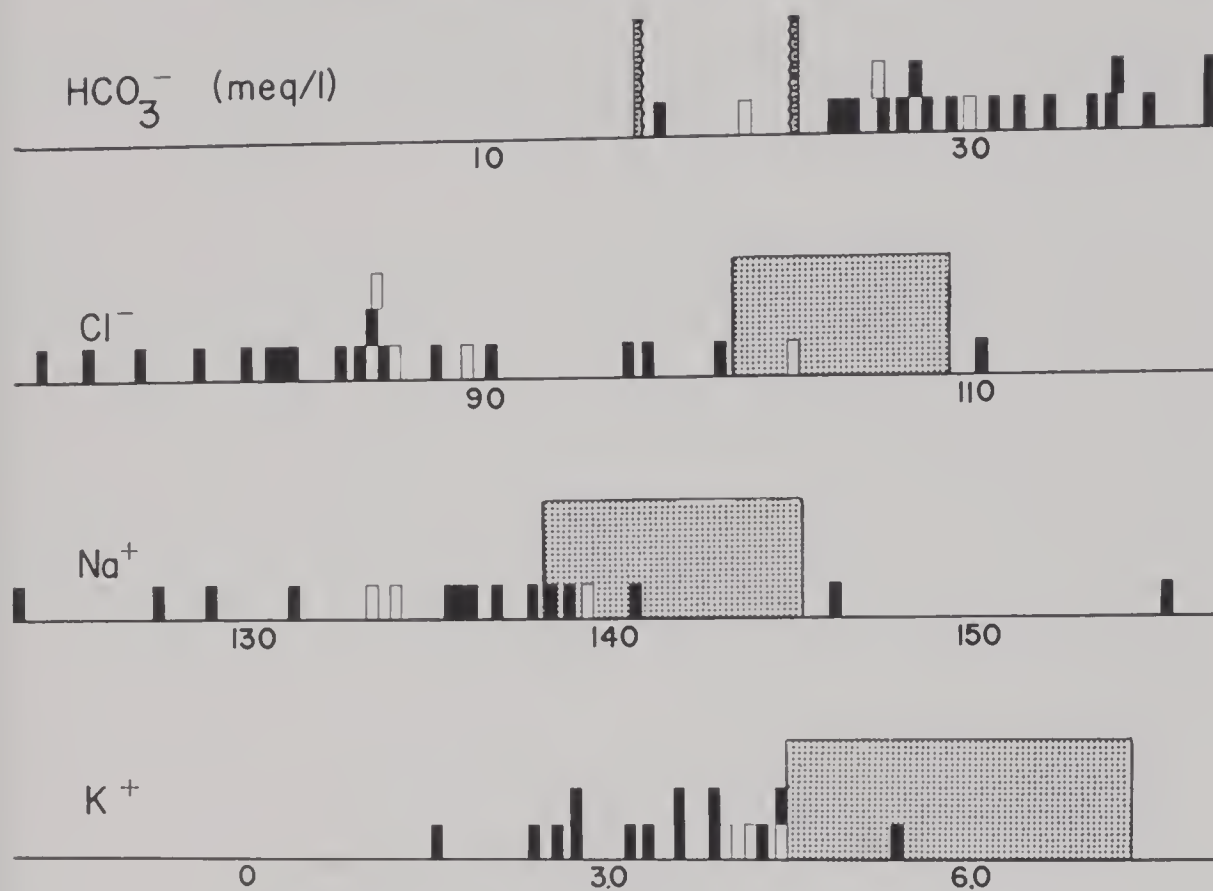


FIG. 6-6. SERUM ELECTROLYTES IN 23 INFANTS WITH PYLORIC STENOSIS PRIOR TO SURGICAL RELIEF OF THE OBSTRUCTION

Solid columns identify male infants.

The plotted values represent the most marked changes found during serial day to day measurements and indicate that hypochloremia and alkalosis are frequently though not invariably present. The changes in sodium and in potassium are less marked but they nonetheless indicate a tendency to a decrease in the concentrations of each of these constituents.

The shaded background depicts the  $\text{Cl}$ ,  $\text{Na}$ , and  $\text{K}$  findings in 95 per cent of 61 to 90 normal infants (i.e. mean  $\pm$  2 S.D.) 0 to 6 weeks of age as described in chapter 4. The values for bicarbonate are taken from a much smaller series of infants but are in keeping with the findings of others. (Danowski *et al.*, unpublished data.)

Electrolytes are lost in the same proportions as those prevailing in the extracellular fluid, the levels will not change. On the other hand if water losses predominate the concentrations will rise. Finally, if electrolyte losses are the greater, hypotonicity supervenes. In all three of these eventualities the absolute amount of body electrolyte has been decreased.

In summary, therefore, ingestion of food or fluids stimulates an outpouring of gastric secretions thereby augmenting the volume and the solute content of the ingested materials. This process is physiologic since it occurs regularly in healthy subjects and is followed by subsequent assimilation of the food, the fluids, as well as the secretions. In diseases characterized by vomiting the volume and the electrolyte content of the secretions are greatly increased and subsequent reabsorption does not of course occur. The net

effect is sodium and chloride depletion, metabolic alkalosis, and potassium deficiency superimposed on dehydration and starvation.

#### IV. Diarrhea

Profound changes in body fluids and electrolytes are encountered frequently in the diarrheas of infancy and are occasionally seen in older patients. As in vomiting, these patients also develop various degrees of dehydration and starvation, as well as more specific deficits of body constituents through losses of gastrointestinal secretions. In contrast to gastric juice, the intestinal fluids contain bicarbonate rather than chloride as the predominant anion. Sodium and potassium are again the chief cations. Analyses of diarrheal stools reveal a much higher content of water, sodium, potassium, chloride, and nitrogen than that present in formed stools. The electrolytes which are lost represent either ingested or endogenous material, or both (5a-e).

Evidence from studies in children indicates that the losses from the body

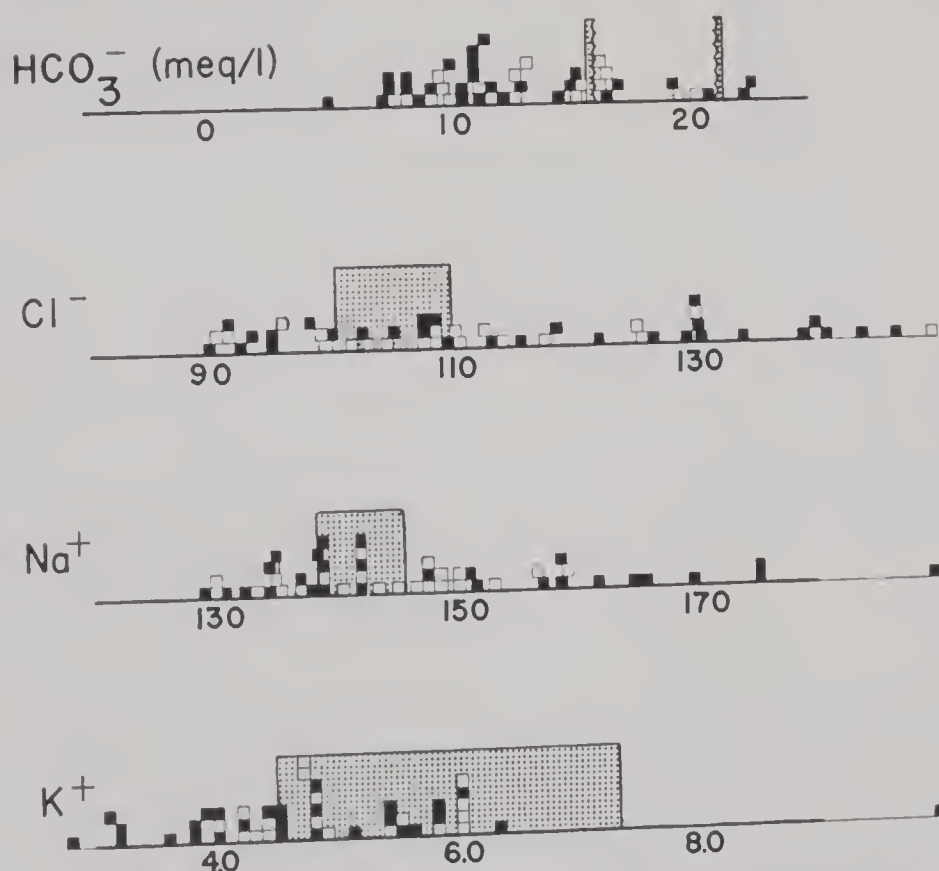


FIG. 6-7. SERUM ELECTROLYTES IN DIARRHEAL INFANTS

The above values (solid squares = males) represent findings at admission or shortly thereafter. It will be noted that in some of the infants the electrolyte values fall within the range of normal. The hypernatremia, hyperchloremia, hyperkalemia, and acidosis were encountered in patients with the protracted or the more intensive forms of the illness. The shaded background indicates findings in normal infants as described in chapter 4. (Danowski *et al.*, unpublished data.)

can be minimized or even cancelled by sufficient increases in the intake of these constituents even though diarrhea persists (5f, g). This is not, however, the ordinary therapeutic practice and hence negative balances together with deficits of body water are the usual finding in patients with diarrhea.

Figure 6-7 shows in infants with diarrhea the pattern of electrolytes shortly following admission. The infants with the more severe and protracted forms of the disorder invariably show marked dehydration which raises the concentration of extracellular electrolytes even though actual deficits exist (see fig. 20-1). This explains the marked hyperchloremia, hypernatremia, and hyperkalemia. The accompanying metabolic acidosis is related to losses of bicarbonate in the stool, to starvation with consequent accumulation of ketone bodies, to renal failure, and to hyperchloremia.

As mentioned earlier, diarrhea in adults is a much less severe disease. Adult subjects show a greater ability to maintain the fluid of the body within normal concentrations and hence the deficits which are contracted are not, in the early phases at least, accompanied by hyperelectrolytemia. Extensive deficits can however develop in dysentery, cholera, ulcerative colitis, and in the diarrhea of nontropical sprue (6a-c). Potassium is also lost via the red cells which are so frequently present in stools of the first three categories of such patients. Potassium deficits have also been reported following chronic use of laxatives (6d).

## V. Sweating

Analyses of sweat reveal a variable though usually high content of sodium and chloride and lesser amounts of potassium and nitrogen. Hence any illness characterized by fever and sweating will augment the extrarenal losses of these electrolytes. If these are not replaced, deficits will ensue.

Some of the factors which influence the electrolyte content of sweat have been identified. Thus acclimitization to tropical temperatures involves decreases in salt output; adrenocortical hyperactivity decreases sodium in sweat while insufficiency raises it (7a-c). In mucoviscidosis, a pancreatic-respiratory tract disorder in children, the sweat glands put out sodium in larger amounts than usual and render these patients especially susceptible to deficits (7d).

## VI. Renal Function and Dysfunction

The role of the kidney in the development of deficits of body fluid and electrolytes can be quickly delineated.

### A. Water

The inevitable loss of some body water even when urine formation is occurring under the maximal stimulus of antidiuretic substances, has already



been described in the discussion of the dehydration reactions. In chronic renal disease the kidney may fail to conserve water to the extent that this becomes the chief route of loss, surpassing the insensible perspiration in this regard.

Obviously with injury to the hypothalamic-hypophyseal system which elaborates these humoral antidiuretic agents, or with kidneys incapable of responding to them, much larger amounts of filtered water will be put out in urine as diabetes insipidus develops. Deficits need not occur, of course, if a sufficient intake of water is provided.

### *B. Sodium and Chloride*

The normal kidney will conserve sodium and chloride in case of need, provided an adequate supply of adrenocortical steroids is available. On the other hand, renal sodium and chloride wastage is a constant feature only of classical Addison's disease and occurs only infrequently and even rarely in chronic nephritis. This latter fact is not generally appreciated. Such erroneous views stem from the fact that the lowering of serum concentrations of sodium and of chloride which occurs so often in patients with renal disease is taken to indicate salt wastage. The actual mechanisms involved are discussed in greater detail in chapter 12 where it is pointed out that in the early phases of recovery from acute tubular injury, as in lower nephron nephrosis, temporary true salt wastage may be present.

The effect of mercurial diuretics and of carbonic anhydrase inhibitors in increasing sodium and chloride output is discussed in chapter 9. These may contribute to or be responsible for deficits of these two electrolytes.

### *C. Potassium*

It has already been indicated in chapter 5 that renal conservation of potassium is not adequate to prevent undue losses of body potassium during periods of illness characterized by stress and inadequate intake. This is clearly illustrated by the continued renal excretion of potassium in the absence of intake, figure 6-8, noted in a group of adult subjects with gastrointestinal diseases (8a). However, since simple deprivation of potassium in normal subjects leads to renal conservation in the course of a few days (8b), it is probable that stress leading to adrenocortical hyperactivity is an additional factor in the production of deficits large enough to be of clinical significance. These factors result in potassium deficits in a host of otherwise unrelated disease states.

Other situations known at present in which the kidney may contribute to deficits of potassium are the occasional cases of chronic renal disease and convalescent lower nephron nephrosis with unduly large urinary output of

potassium, suggesting tubular secretion of the ion, as well as those patients receiving mercurials or carbonic anhydrase inhibitors.

#### *D. Phosphate and Other Electrolytes*

Undue losses of phosphate are encountered in patients with hyperparathyroidism or excessive amounts of vitamin D as a consequence of the renal effects of these agents as described in the preceding chapter. In diabetic coma the cells lose large amounts of organic and soluble phosphorus and serum inorganic levels decline markedly as a consequence of renal excretion (chapter 15).

Renal losses of phosphate which ultimately result in deficits of this constituent occur only rarely in renal disease, as in the DeToni-Fanconi syn-

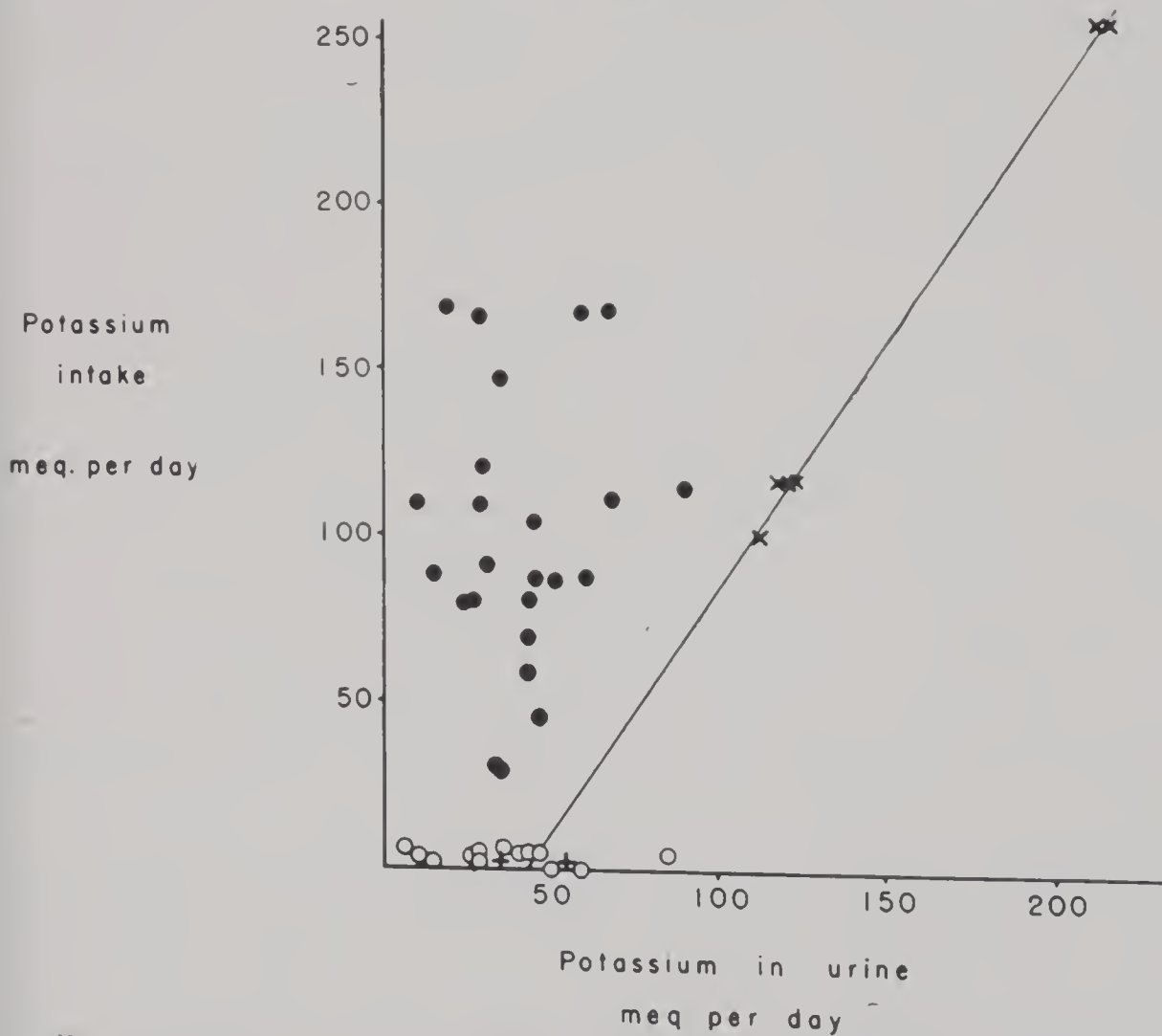


FIG. 6-8. RELATION OF DAILY RENAL EXCRETION OF POTASSIUM TO INTAKE

Circles represent patients with potassium deficiency but with normal kidneys, on low intakes of the ion (open circles) and on high intakes (solid circles). The crosses represent normal control subjects. On a very low intake of potassium both the patients and the controls continued to excrete significant amounts of potassium. (From Tarail and Elkinton (8a).)

drome. These are discussed in chapter 12. In almost all other types of renal failure the excretion of inorganic phosphate is inadequate and hyperphosphatemia develops.

Conditions which result in deficits of calcium, magnesium, protein or other electrolytes are discussed in relationship to particular disease entities, as well as in Part IV which deals with therapy.

**SUMMARY:** Many disease states which are otherwise unrelated have certain features in common such as starvation, dehydration, vomiting, diarrhea, sweating, and renal dysfunction. These symptoms can exert profound influences upon the volume and composition of body fluids and solutes. Thus, starvation produces negative balances of body protein and sets free cell constituents such as nitrogen and potassium. Dehydration sets in motion transfers of fluids from cells to extracellular fluid so that the water deficit is shared by all phases of the body fluid. Vomiting or diarrhea can lead to deficits of body water and electrolytes in addition to interfering with the assimilation of food and fluids. The output of electrolytes in sweat and urine also affect the net balances of body constituents in disease states.

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## Chapter 7

# THE PHYSIOLOGIC EFFECTS OF WATER AND ELECTROLYTE DEFICITS AND THEIR TREATMENT

The decrease in total body water which ensues in dehydration has been discussed in detail in chapter 5. It was pointed out that dehydration induces transfers of water and certain solutes between the various body compartments. In discussing the physiologic concomitants of dehydration the importance of such movements from cells to extracellular fluid in protecting the dehydrated patient from a dangerous depletion of the plasma volume will be emphasized.

### I. Dehydration: Circulatory and CNS Changes

Recollection of the routes of water excretion in partial or total deprivation points up the fact that the *immediate* loss, both renal and extrarenal, occurs from the extracellular compartment. Within a moment however adjustments take place which apportion the water deficit between the cells and the extracellular fluid. It has already been pointed out that these are mediated through: a) a transfer of water from cells in response to the increased osmolarity of the extracellular fluid, b) release of cell potassium with further inevitable movements of cell water, and c) decreases in the osmotically active cell base (as discussed in the preceding chapter), with the release of additional increments of cell water to replenish the extracellular fluid. Consequently, any loss of water from the body is apportioned among all of the fluid compartments. This is of particular importance in protecting the organism against marked depletion of any single compartment.

With continued dehydration, however, the adjustments which have been described will no longer suffice to defer the onset of the physiologic effects of dehydration and hypertonicity. Simple dehydration of the type under discussion has been shown to result, though sporadically it is true, in circu-

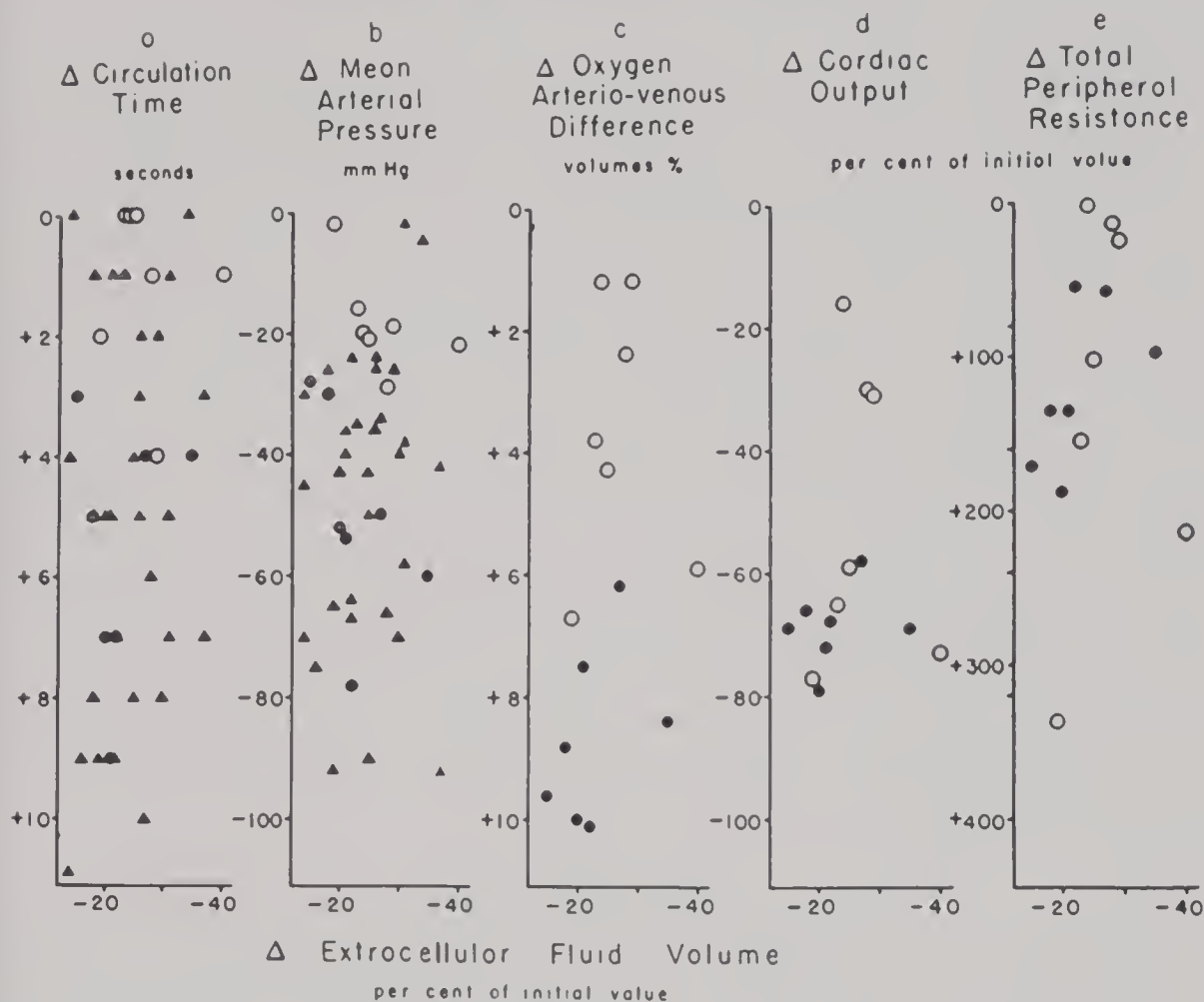


FIG. 7-1. COMPARISON OF HEMODYNAMIC CHANGES IN SALT DEPLETION WITH THOSE IN WATER DEPLETION IN DOGS

Percentile changes in extracellular fluid volume are plotted along the abscissae, the hemodynamic measurements are plotted along the ordinates. Open circles represent water depletion. Closed figures represent salt depletion.

Salt depletion in contrast to water depletion is characterized by a greater increase in circulation time, a greater fall in mean arterial pressure, and a greater rise in oxygen arteriovenous difference. There is no consistent difference between the two groups in the changes in cardiac output and in total peripheral resistance. (From Elkinton *et al* (1c).)

latory changes. These are limited to moderate decreases in the cardiac output, minor prolongation of the circulation time, and slight falls in blood pressure. In general, therefore, it would appear from both experimental data and clinical observations that in hypertonicity ensuing from simple dehydration collapse of the circulation does not occur with any regularity (fig. 7-1). This is in all probability related to the fact that extracellular and plasma volumes are relatively well-maintained at the expense of cell water through the transfer mechanisms which have been described (1a-h).

In contrast to these occasional and minor circulatory changes mental confusion has been noted with considerable regularity in individuals with de-

hydration hypertonicity. It has been described in subjects undergoing voluntary deprivation of water, in castaway sailors on limited water supplies, as well as in patients (2a-e). In a sense this is not a surprising development since the cells of the nervous system share both the general dehydration and hypertonicity and are among the first tissues to show functional change when metabolic constituents such as oxygen and glucose are not available in needed amounts. The deleterious effects of cell dehydration have also been observed in animals treated with the hypertonic saline (see fig. 2-8). In such animals the respirations cease at a time when the pulse is full and bounding and the circulation well-maintained (3). Presumably the same events occur in castaways who drink and retain sea water, or in patients deprived of water (4a). With respect to the latter the observations of Broch are of particular interest: hypertonicity and hypernatremia developed in patients hospitalized following a cerebral vascular accident, but treated with less than adequate amounts of water (4b). It can be readily seen that respiratory failure in this category of patients would be assumed to represent a sequel of the cerebral lesion whereas it might well be related to progressive dehydration.

## II. Salt Depletion

Recognition of sodium deficits in patients is of major importance in view of the accompanying physiologic changes. These are most readily described by considering those experimental and clinical situations in which sodium is lost without significant alteration in the total volume of body water.

### *A. Experimental and Clinical Examples of Salt Depletion*

The classic experiments of Darrow and his colleagues serve this purpose well (5a-c, 1c). In such studies a solution of five per cent glucose in water is introduced into the peritoneal cavity; sampling of the peritoneal contents at intervals indicates that some glucose does enter the body fluids but that extracellular electrolytes also move much more rapidly into the peritoneal cavity. Such transfers reflect movements of solutes in accordance with their specific coefficients of diffusion and with the concentration gradients on the two sides of a permeable membrane. The net effect of these solute exchanges is a depletion of extracellular electrolytes and of sodium and chloride in particular (fig. 7-2).

### *B. Hemodynamic Effects of Salt Depletion*

The circulatory changes are a consequence of the fact that the differential osmotic pressure of extracellular fluid is primarily dependent upon sodium and chloride. The quantitative contribution of the remaining cations is, from this viewpoint, less significant. Hence any process which reduces



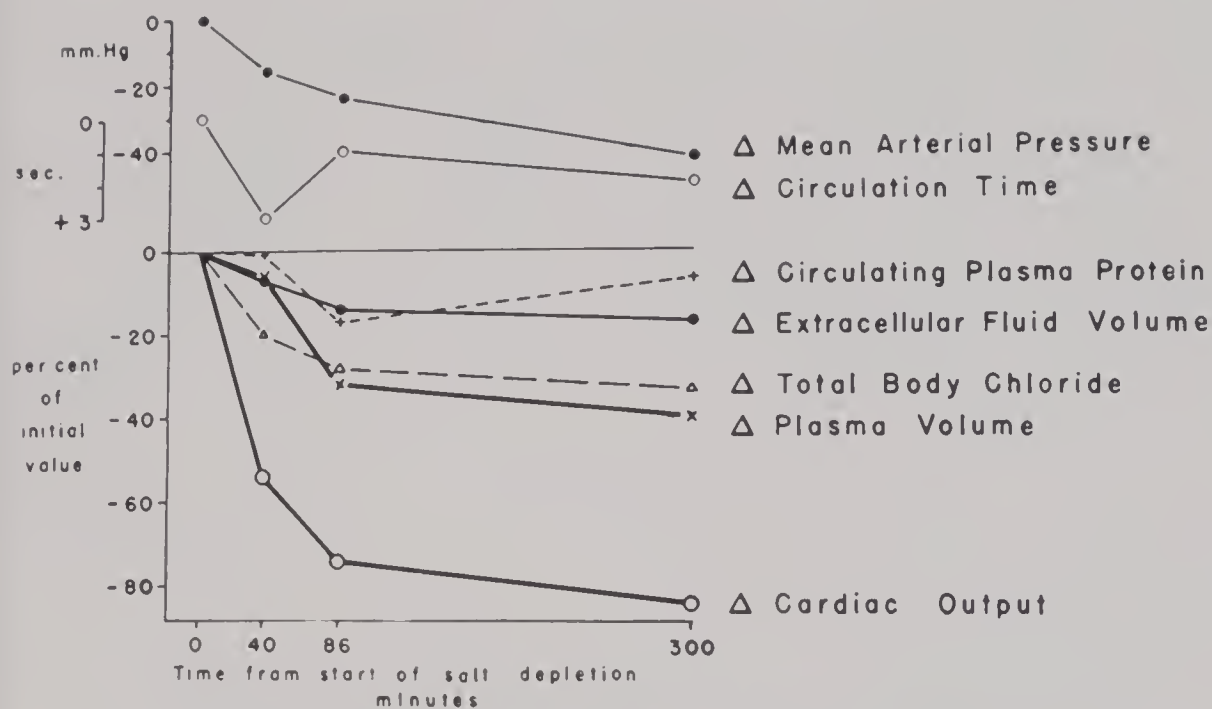


FIG. 7-2. RELATION OF CHANGES IN HEMODYNAMICS TO CHANGES IN BODY FLUIDS IMMEDIATELY FOLLOWING THE ONSET OF SALT DEPLETION IN A DOG

The removal of extracellular electrolytes reflected in the hypochloremia produced circulatory collapse characterized by a drop in blood pressure, prolongation of circulation time, and a fall in cardiac output. This was associated with losses of extracellular and plasma volumes and of circulating plasma protein. It is to be noted that the drop in cardiac output preceded the fall in plasma volume. (From Elkinton *et al* (1c).)

the extracellular sodium and chloride will necessarily lower the osmotic pressure in this compartment. Such a drop is followed in turn by movements of extracellular water into the cells. The latter become swollen at the expense of the interstitial and plasma water. Furthermore, this abstraction of sodium is promptly followed by a loss of circulating plasma protein and of albumin in particular and hence a further decline occurs in the volume of the plasma (1c, 5d-h). This is shown in figure 7-3. This is reflected in hemoconcentration and increased viscosity of the blood and plasma. These changes produce a decline in the cardiac output, a decrease in the venous return, a drop in the blood pressure, and a prolongation of the circulation time (fig. 7-2). Hence circulatory collapse is the inevitable result of extensive losses of extracellular sodium. Since such circulatory collapse includes the renal circulation, renal insufficiency with oliguria and azotemia is a common sequel of sodium depletion. The clinical analogues of these types of experiments occur during the administration of glucose solutions by hypodermoclyses (5i-k) or during gastrointestinal lavage with nonelectrolyte solutions. The first of these is illustrated in figure 7-4.

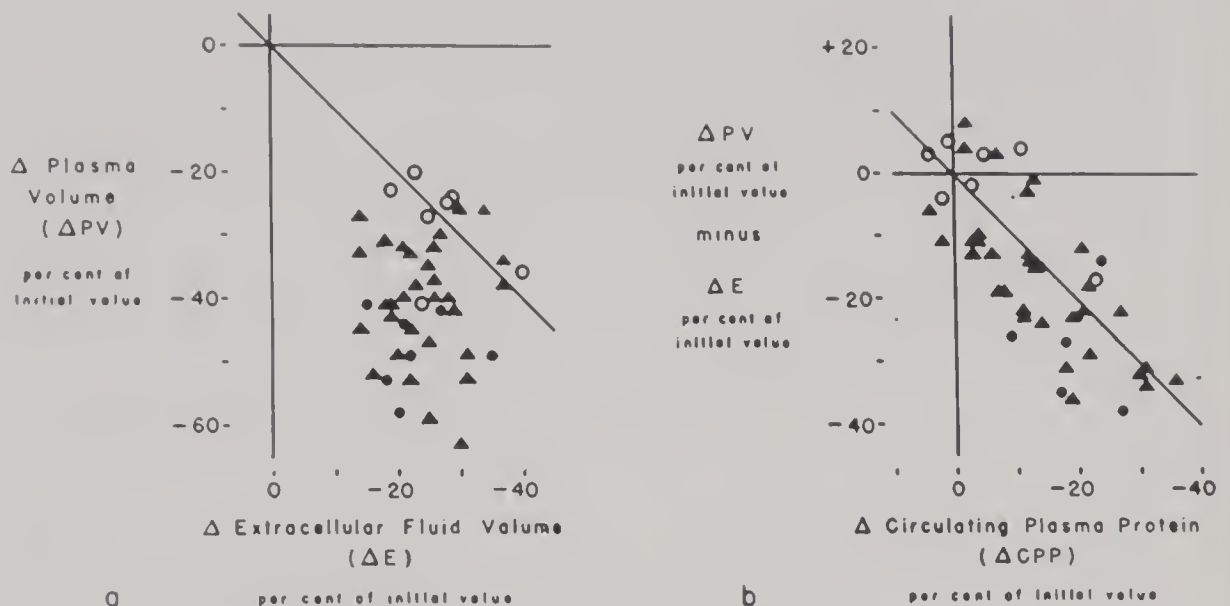


FIG. 7-3. COMPARISON OF (A) PERCENTILE CHANGES IN EXTRACELLULAR FLUID VOLUME WITH THOSE IN PLASMA VOLUME, AND (B) THE DIFFERENCE BETWEEN THESE TWO VALUES AND THE PERCENTILE LOSS OF TOTAL CIRCULATING PLASMA PROTEIN

Open circles represent water depletion. Closed figures represent salt depletion. In water depletion, the fall in plasma is roughly proportional to the fall in extracellular fluid volume. In salt depletion, the decrease in plasma volume exceeds the decrease in the volume of extracellular fluid (a). Disproportionate drops in plasma volume correlate well with loss of total circulating plasma protein (b). (From Elkinton *et al* (1c).)

### C. Dehydration and Salt Depletion: Experimental and Clinical

In contrast to the above illustrative experiments most clinical situations are characterized by concurrent losses of sodium and of water, though not necessarily in the proportion in which they exist as body constituents (6a-f). There is no evidence however that the superimposition of dehydration upon salt depletion in any way ameliorates the circulatory effects of the latter. As a matter of fact the combination often results in further deterioration of cardiovascular efficiency. This is clearly evident from certain animal experiments in which salt depletion was first produced by the Darrow-Yannet technic. This resulted in a loss of body sodium without a net loss of body water, though the characteristic shift of extracellular water to the cellular space occurred; the circulatory efficiency decreased in characteristic fashion. The infusion of concentrated urea into these animals resulted in a diuresis, thereby superimposing dehydration upon the salt depletion. This corrected the tonicity of the body fluids, but the cardiac output, mean arterial blood pressure, and the speed of the circulation all decreased further (7). This sequence of events is shown in figure 7-5.

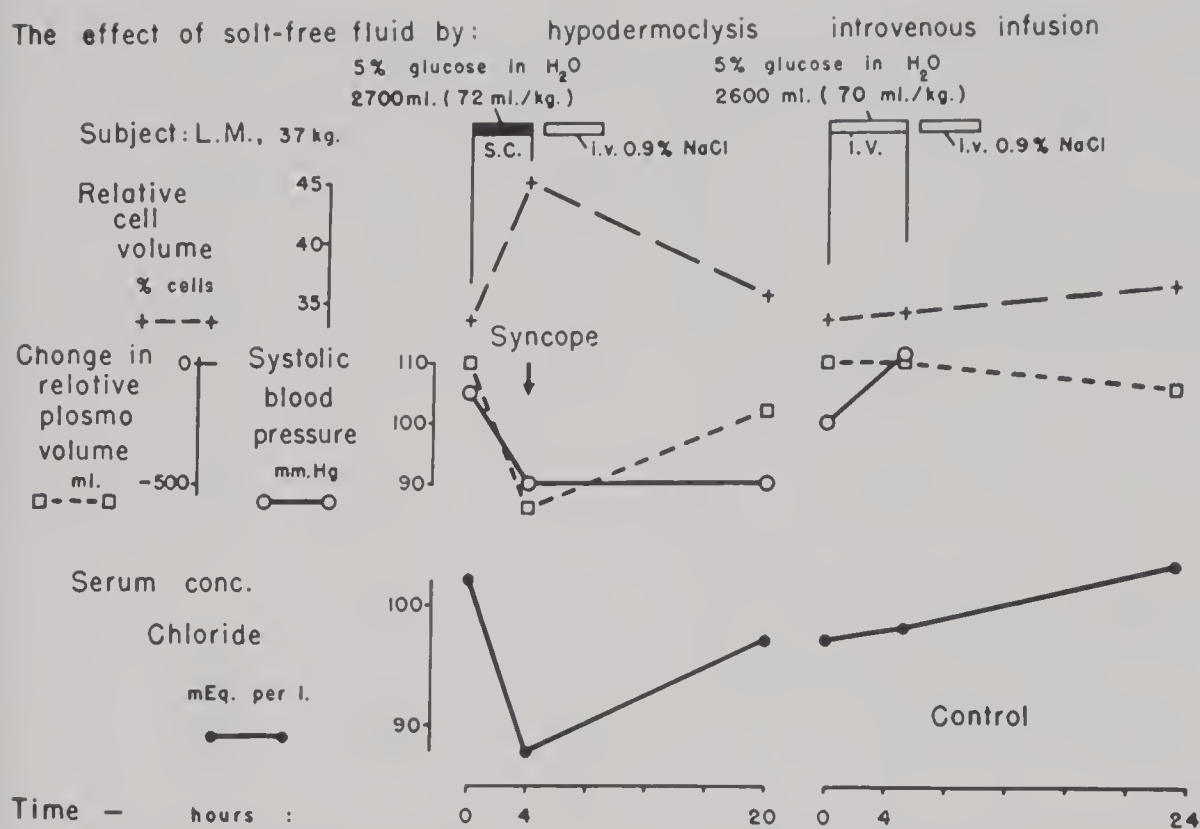


FIG. 7-4. PRODUCTION OF SHOCK BY THE SUBCUTANEOUS INJECTION OF SALT-FREE FLUID

The subcutaneous administration of a hypodermoclysis of 2700 ml. of five per cent glucose in water to a nondepleted hospitalized patient produced hypochloremia, hemoconcentration and diminished plasma volume, hypotension and syncope on rising to the upright position. These are evidences of peripheral vascular collapse resulting from diffusion of extracellular electrolyte into the subcutaneous pool of glucose and water. A similar solution when given *intravenously* into the same subject on a later date produced no such effects. (From Danowski, Winkler, and Elkinton (5i).)

### III. Potassium Deficiency: Its Origins and Manifestation

In clinical usage the terms hypokalemia and hypopotassemia are taken to indicate a lowering in the concentrations of this ion in serum or plasma below the usual range present in health, even though the words themselves refer to levels in blood. As illustrated in chapter 4 the lower limits of these sets of values are 3.3 milliequivalents per liter in growing children, in young adults, and in old men and women and above four milliequivalents per liter in newborn infants (8a). The fact that all of the potassium in serum is ultrafiltrable suggests that it is present entirely in the ionized form (8b). Hence lowered serum levels of this electrolyte can be taken to reflect comparable changes in the potassium concentration of the extracellular fluid as a whole, i.e., in the interstitial spaces as well as in the plasma. Since such



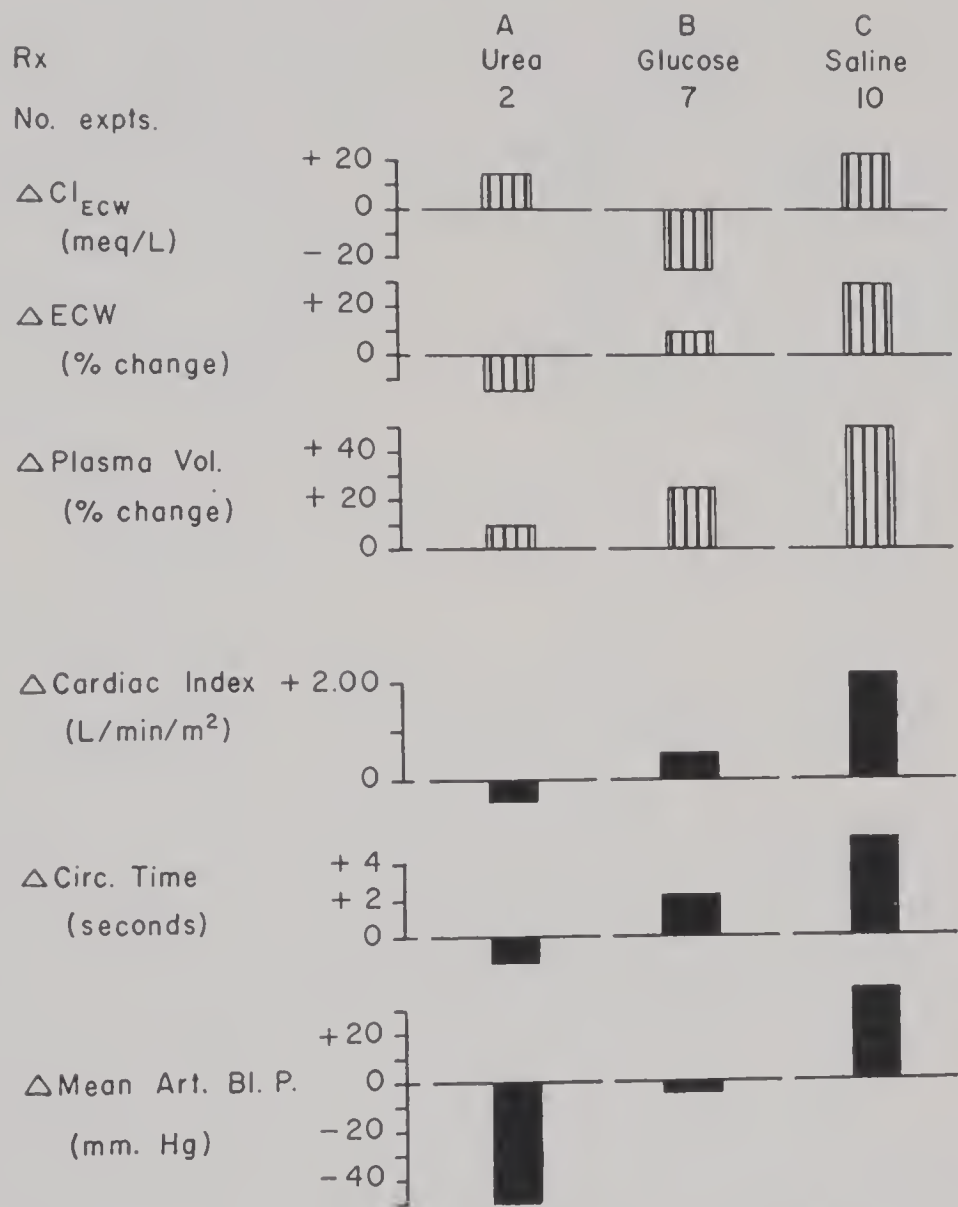


FIG. 7-5. CHANGES IN CIRCULATORY DYNAMICS FOLLOWING VARIOUS TYPES OF TREATMENT OF SALT DEPLETION SHOCK IN DOGS

Each column represents the mean value for the number of experiments indicated. The changes shown were produced in animals already in salt depletion shock. In such a state, restoration of concentration alone by urea diuresis (column A), or of volume alone by glucose infusion (column B), failed to improve the circulation. Restitution of both volume and concentration by infusion of saline (column C) was followed by prompt recovery from the shock state. (From Elkinton *et al* (7).)

lowered levels of extracellular potassium may be present without any change in the total amount of extracellular or cellular potassium, they may reflect transfers of potassium into cells (8c), or they may point to losses of cellular and extracellular potassium.

A. Low Serum Potassium Levels with Extracellular and Cellular Potassium Intact

The administration and retention of water or of glucose solutions will dilute the extracellular and the cellular fluids of the body. If potassium is

not present in such solutions the levels of this ion will decrease in cells as well as in the extracellular fluid. Under these circumstances hypokalemia may appear even without any external losses of this ion and without evident change in its compartmental distribution.

Such a change in body potassium concentration will occur in those patients in whom the excretion of water loads is defective, i.e., in patients with oliguria or anuria as in acute tubular damage or lower nephron nephrosis or, to a transient or limited extent, in those patients with adrenocortical insufficiency, cirrhosis with ascites, or congestive heart failure.

#### *B. Low Serum Potassium Levels as a Result of Movements of Extracellular Potassium into Cells*

A number of mechanisms which result in the movement of potassium into cells have been recognized (fig. 7-6). Perhaps the most fundamental of these is the incorporation of this indispensable ingredient of cells during the processes of cell growth or repair. In this regard substances such as testosterone which accelerate protein anabolism have been shown to induce these transfers (8d).

Another set of basic processes which are accompanied by transfers of potassium into cells are those related to carbohydrate metabolism. It has been shown, for example, that the utilization of sugar by blood cells or by tissue preparations *in vitro* lowers the potassium content of the suspending medium (8e, f) (see fig. 3-2). The disposal of exogenous carbohydrate frequently, though not invariably, lowers the extracellular potassium levels (8g). This is attributable in part to the deposition of potassium with glycogen in the liver (8h). Insulin given intravenously in amounts as little as 0.1 unit per kilogram of body weight almost invariably lowers the serum levels

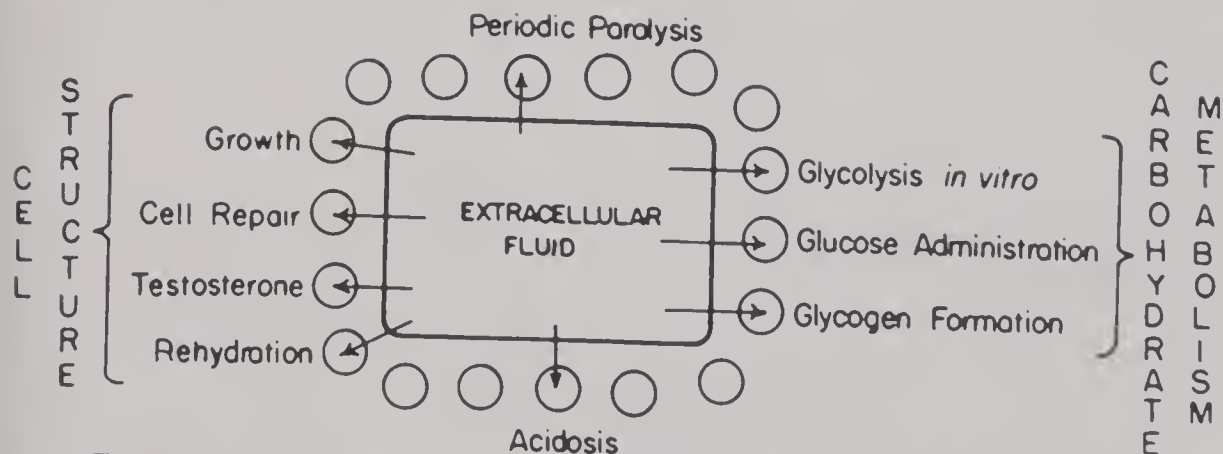


FIG. 7-6. HYPOKALEMIA AS A CONSEQUENCE OF POTASSIUM TRANSFERS INTO CELLS

The various known processes which result in a movement of extracellular potassium into cells are listed together with the one disease entity, periodic paralysis, in which hypokalemia results from transfers of extracellular potassium into cells.

of potassium (8i). This presumably reflects participation of this ion in the phosphorylation of glucose and its entry into cells.

There remains a series of miscellaneous and apparently unrelated circumstances in which hypokalemia results from transfers into cells. Thus progressive dehydration is known to result in losses of cell potassium and hence it is not surprising to find that rehydration reverses this trend (8j). Alterations in the pH of body fluids may induce potassium shifts: alkalosis removes potassium from cells whereas acidosis induces transfers into cells (8k). Finally, in familial periodic paralysis the extracellular potassium usually drops prior to or during a seizure (see fig. 16-1). Since this is usually not attributable to losses of the ion in urine, it points to a segregation of extracellular potassium in cells (8l). It is interesting to note, in view of the previous comments on carbohydrate metabolism and potassium transfers, that heavy meals or insulin or glucose administration can precipitate such attacks in afflicted individuals.

### *C. Deficits of Body Potassium as a Result of External Losses*

Body potassium, both extracellular and cellular, can be lost via renal as well as extrarenal routes (fig. 7-7).

The continued or increased urinary output of this ion in patients not receiving adequate maintenance amounts of potassium inevitably results in

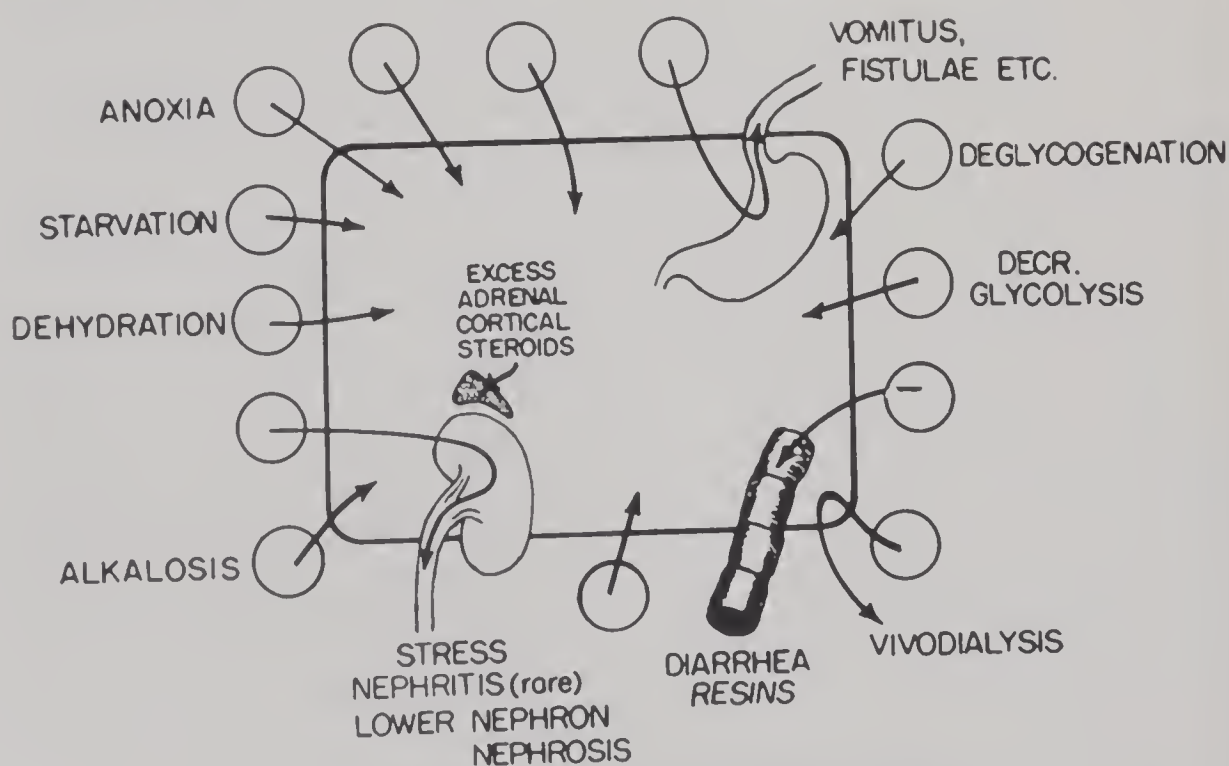


FIG. 7-7. ETIOLOGY OF POTASSIUM DEFICITS

The known processes which result in transfers of cell potassium to extracellular fluids and of extracellular potassium to the external environment are listed in the figure.



depletion. It has been suggested that this reflects an inherent inability of the kidney to conserve this ion during periods of potassium deprivation (8m). Recent studies in animals and in humans indicate that in health more precise renal conservation of potassium can be evoked by potassium-free regimens (8m-p). Hence the renal losses of potassium which occur with gastrointestinal disease, poliomyelitis, and a host of other diseases are mediated through an inadequacy of the renal conservation response, perhaps as a consequence of changed adrenocortical activity.

Increased renal losses of potassium can also be induced by ACTH and adrenocortical type steroids, by mercurial diuretics, and by carbonic anhydrase inhibitors. They are known to occur in the recovery phase of some patients with lower nephron nephrosis as well as in a limited number of patients with chronic renal disease (see chap. 12). In the last of these two categories the mechanism of loss may well be related to an undue tubular secretion of this ion (8r).

Extrarenal losses of potassium are incurred via vomiting, gastrointestinal drainage or lavage, diarrhea, cation exchange resins, or vivodialysis (8q).

#### *D. Reliability of Lowered Concentrations of Serum Potassium as an Index of Potassium Depletion*

It is immediately obvious from the preceding section that the simple presence of lowered plasma or serum levels of potassium does not establish the existence of potassium deficits outside or inside of cells. However, if dilution and transfers of potassium into cells can be excluded, it is true that the small portion of body potassium present in serum or plasma often reflects similar changes within the larger pool of this ion in cells (8k). Hence such a finding should arouse a high index of suspicion of potassium deficiency.

On the other hand the presence of normal or even high concentrations of serum potassium do not exclude this possibility, since dehydration will mask such deficits. This is especially clear from studies in infant diarrhea and in diabetic coma (8q). Under such circumstances the understanding of the basic physiology of these disorders which clearly indicates that deficits are incurred should take precedence over the absence of hypokalemia.

#### *E. Biochemical and Physiologic Changes in Potassium Depletion*

Rather regularly deficits of extracellular and cellular potassium are accompanied by hyponatremia and alkalosis, as discussed in detail in chapter 11. This new steady state represents the net effect of an undue loss of acids from the extracellular space by transfers into cells or by excretion via the urine (8k) (see fig 11-15). It is *per se* of no known or established clinical significance save that it does serve to alert the physician to the presence of

potassium deficits. In this regard it should be remembered that the superimposition of renal failure or starvation will mitigate or replace the metabolic alkalosis with a metabolic acidosis. This occurs, for example, in the prolonged vomiting of pyloric stenosis.

Deficits of cellular potassium, produced by a number of means, lead to microscopic necrosis of skeletal and cardiac musculature (8q) and presumably interfere with cell integrity and function. These may well be the most important deleterious effects of potassium depletion since they are crucial determinants of survival or recovery. Experimental animals and patients with hypokalemia may develop electrocardiographic alterations consisting of various degrees of T wave depression and the so-called Q-T prolongation, shown in figure 7-8, as well as muscular paralysis or paralytic ileus (8s). The studies of Surawicz and Lepeschkin indicate that the widespread belief that Q-T is prolonged is erroneous, arising from a confusion of the T and U wave or from other factors (8t) (see also fig. 15-12).

The above findings are not invariable concomitants of low potassium levels in plasma and hence serve to emphasize the incompleteness of our knowledge. Are the symptoms and signs which develop in such patients correlated with the levels of either extracellular or cellular potassium alone? Is the ratio of the two the determining factor? Does the ionization of cell potassium play a role? What about the associated electrolyte disorders that are frequently present in these patients, or of the medications which are given? In regard to the last two of these it is important to note that hypokalemia and hypocalcemia tend to mask one another symptomatically (8u, v), and that hypokalemia evokes the toxic manifestations of digitalis in patients in whom the maintenance dosage had previously been adequate (8w, x). These observations point up the need for precise observations which will explain the variable incidence of physiologic changes with comparable degrees of hypokalemia.

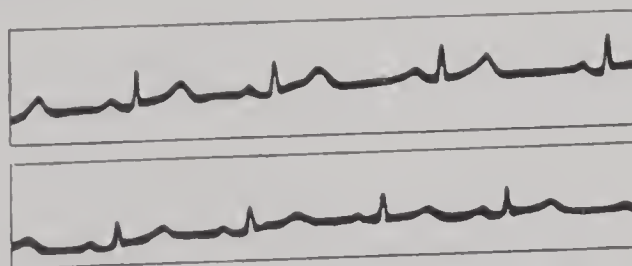


FIG. 7-8. ECG CHANGES IN EXPERIMENTAL HYPOKALEMIA

In this subject, J. H., insulin was given intravenously with a drop in potassium from 4.6 to 4.1 mEq. per l. in the course of 30 minutes. This was accompanied by a flattening of the T wave, the "so-called" prolongation of QT (but see Surawicz and Lepeschkin (8t)) and a decrease in the amplitude of the QRS complex and the P wave. It should be pointed out however that other electrolytes changed as well, including serum inorganic phosphorus, and that at this time their contributions to the ECG changes, if any, have not been defined. (Danowski *et al.*, unpublished data.)

### F. Exchanges of Sodium for Cell Potassium in Potassium Depletion

As indicated in earlier chapters, a small portion of sodium is present in the cells of various tissues. Evidence for this rests upon individual tissue analyses and upon studies of the volume of distribution in the intact organism of the isotopes of sodium as described in chapter 3. The differential distribution of sodium and potassium has already been discussed and appears to depend upon the active transport of sodium out of cells by energy obtained from cellular metabolism (see fig. 1-10). This must be a constant pumping out process in a dynamic equilibrium which becomes disturbed in many disease states, since much evidence has accumulated to indicate that large changes in this portion of body sodium occur. Transfers of intracellular sodium sometimes bear a reciprocal relation to those of cellular potassium (8c); at other times, the movements of these two intracellular cations appear to be quite independent of each other (fig. 7-9). Reciprocal exchanges of sodium and potassium were early described by Bunge (8y) and have been elaborated upon by Gamble (8z); an experimental example of the phenomenon is shown in figure 7-10. Clinical examples are to be found in figures 3-15, 11-9, and 22-1.

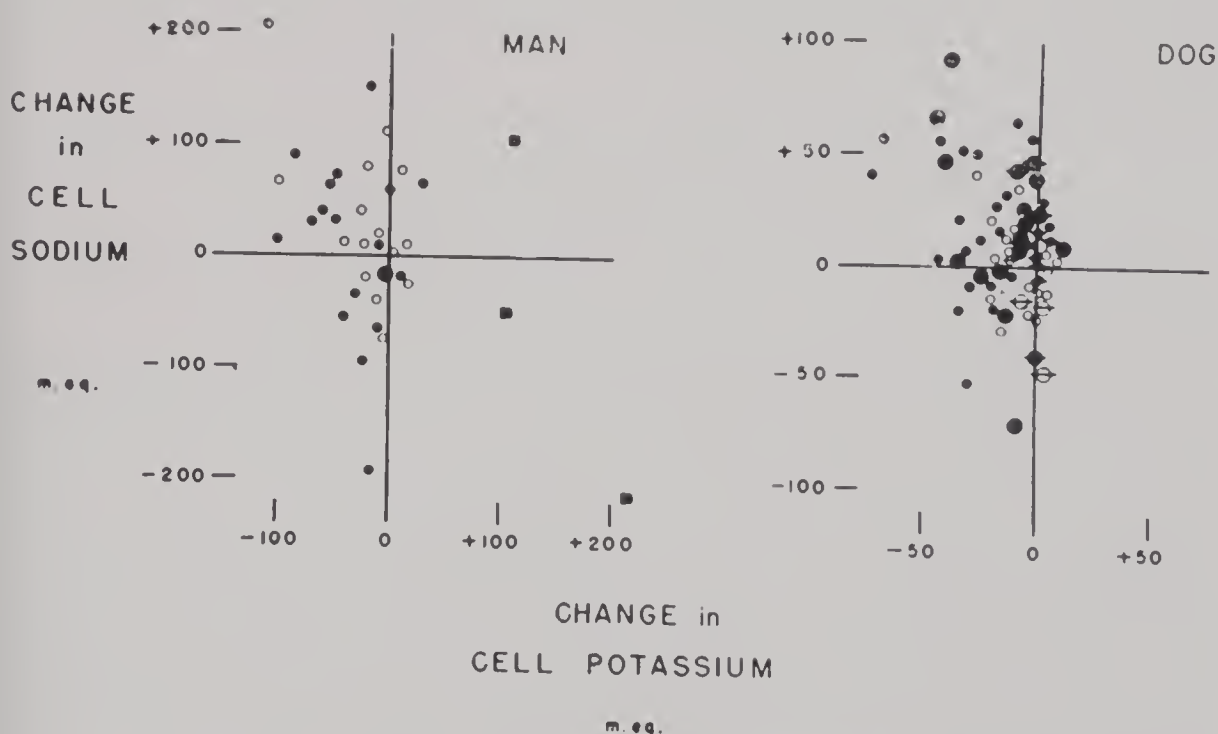


FIG. 7-9. EXCHANGES OF SODIUM FOR POTASSIUM WITHIN CELLS

Though in general losses of cell potassium were accompanied by a gain of sodium (left upper quadrant of each of the above figures), this was not an invariable occurrence under certain experimental conditions in man and dog. (From Elkinson *et al* (8c).)



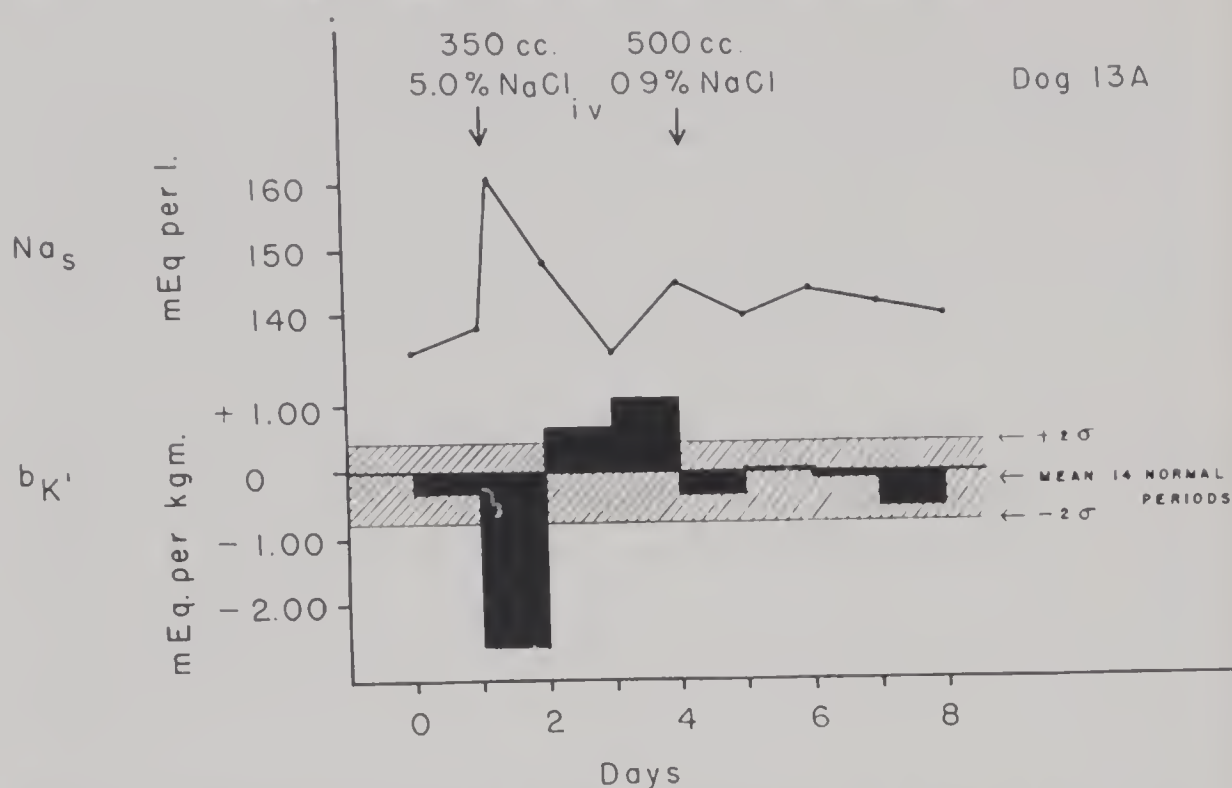


FIG. 7-10. RECIPROCAL LOSS OF POTASSIUM FOLLOWING THE EXPERIMENTAL INJECTION OF HYPERTONIC, BUT NOT ISOTONIC, SODIUM CHLORIDE SOLUTION

Effects are shown on the serum sodium concentration ( $Na_s$ ) and on the balance of potassium in excess of nitrogen ( $b_{K'}$ ), as observed in a dog on a constant meat diet and in nitrogen and potassium equilibrium prior to the salt infusion. (From the data of Elkinton and Winkler (8j).)

#### IV. The Applications of Principles of Water and Electrolyte Replacement to Problems in Clinical Practice

This subject will be discussed in great detail in the last four chapters of this book. The material that follows represents an attempt at orientation in terms of general principles rather than specific procedures.

Several practical questions immediately arise in attempts to reconstitute the concentrations and the total amounts of these various components in cells and in the surrounding fluid. The first two of these relate to the qualitative and quantitative aspects of the problem: "which substances should be replaced and in what amounts?" The immediate response of all those who do not have adequate laboratory facilities, and of many of those who do, is to expect analytical procedures to provide these answers. Unfortunately even when the results are available they may not serve as adequate guides. Several facts contribute to these limitations.

The most important of these is related to the experimental and clinical observation that in the initial phases of depletion concentrations may be maintained within usual limits at a sacrifice of volumes or total amounts (2a, 9a-c). Thus losses of water in deprivation are compensated in part by an increased output of electrolytes in a more concentrated urine of lower

volume. Abstraction of sodium in limited amounts, on the other hand, results initially in a greater flow of urine from which most or all of the filtered sodium has been removed. The net effect of either of these adjustments is to restore or to maintain concentrations at normal levels at the expense of the body stores of the particular constituent under consideration. It is readily evident, therefore, that the mere presence of normal levels of body solutes or water does not guarantee intact total amounts. Moreover, it is even possible to be misled by elevated concentrations into thinking that body supplies are increased whereas a deficiency is actually present. This can be most clearly illustrated by citing the fact that in infantile diarrhea and in diabetic coma, two conditions in which careful studies have established the invariable occurrence of negative potassium balances, the serum potassium levels are frequently high. This is attributable in part to the proportionately greater losses of extracellular water than of extracellular potassium and in part to transfers of potassium from cells to the extracellular fluid. Yet, despite the high serum potassium values, the total stores of this electrolyte have been diminished by the disease processes.

However, for practical purposes it should be pointed out that levels may provide valuable clues in determining therapy. Thus as a general rule, one can state that when depletion is present it is less extensive if the levels are unchanged than if they are lowered or raised. Either of the latter alterations indicate that the initial adjustments which maintain concentrations at the expense of volume or total amounts are either no longer operative, undesirable, or inadequate. This fact in turn suggests that quantitatively a much greater degree of depletion is present.

Having pointed out the limitations and the usefulness of laboratory analyses when such are available, we are still left with the need for a critical evaluation of the pretreatment status of the depleted patient. Irrespective of the laboratory data this can be best done by: a) careful review of the history, b) attention to the physical findings, and c) reliance upon past experiences with regard to the particular disease entity under scrutiny. Thus a story of total deprivation irrespective of whether it is mediated through neglect, or results from coma, etc. is sufficient evidence that dehydration has occurred. Inevitably negative balances of nitrogen and of potassium must have been incurred. If fever and sweating have been present, electrolytes have surely been lost through the skin. Similarly, vomiting, gastrointestinal drainage, or diarrhea would have augmented the losses of water, nitrogen, and electrolytes from the body. In special circumstances additional losses may have resulted from inadequate renal conservation of components of the glomerular filtrate. Hence knowledge of any of those contributory factors is indispensable for adequate estimation of the patient's needs. Warnings should be interposed: a) histories vary in their usefulness

even when reliable, since patients usually have no ready way of quantitating even obvious losses in vomitus, etc., b) interpretation will be especially difficult if the patient has attempted to retain ingested food or fluid. Quantitation in these situations will be materially aided by physical appearances and especially by a knowledge of the body weight before illness compared with that obtained at the time therapy is started. Retracing of antecedent events usually will be simplified substantially if the deprivation or depletion has occurred in a hospitalized patient. In that case the character of the fluids prescribed, nurses' notes concerning the patient, and the more objective data such as body weight changes and relative magnitudes of the intake and output should greatly facilitate the evaluation. Therapy is then designed in accordance with these facts and its effect determined by serial laboratory observations.

### V. Treatment of Dehydration

Every attempt should be made to prevent dehydration. In a sense this can be spoken of as prophylactic therapy. The problem of prescribing adequate fluids to prevent dehydration is encountered in any patient with symptoms which interfere with an adequate oral intake. From the discussions in the preceding chapters it is evident that under such circumstances the chief need is for water to replace insensible losses through the skin and lungs. As has been mentioned earlier, this can exceed 1000 cc. per day in adults.

Another increment of body water is of course lost through the elaboration of urine. The volume which leaves the body via this route will in the main reflect during the first day the antecedent intake. Subsequently the volumes will decline and then stabilize at levels necessary for the excretion of metabolites and electrolytes. The irreducible minimum in the case of individuals with entirely adequate renal function appears to be about 250 to 350 milliliters per day (9d). In view of the fact that urinary solutes do influence urinary volume, and that starvation through cell breakdown releases both nitrogen and electrolytes and increases the production of ketone bodies thereby contributing to the total solutes in urine, foodstuffs should be included in parenteral fluid therapy. Carbohydrate is the best suited for this purpose, since it spares body protein and yields maximal amounts of water on oxidation (2a). The time may come when fat can also be used for this purpose, but the preparations available at present are not ready for general clinical use. Use of protein hydrolysates is justifiable only when the water resources are adequate for the excretion of nitrogenous constituents which escape incorporation into body tissues (9e).

Hence, after adding the excretion of water in urine to the insensible loss, and keeping in mind the metabolic attributes of carbohydrate, it seems



reasonable to suggest the following prescription for fluids for any adult previously well hydrated but currently incapable of an adequate oral intake:

R<sub>x</sub>: WATER WHICH CONTAINS GLUCOSE IN 10 % CONCENTRATIONS, BUT NO OTHER SOLUTES—1500 CC. TOGETHER WITH 200–300 CC. OF 0.9 % SALINE TO BE GIVEN INTRAVENOUSLY, DIVIDED INTO TWO DOSES.

Obviously, if deficits of body water have already developed this volume will only serve to prevent further dehydration. Additional glucose solution must be given to make up pre-existing deficits of body water. Ordinarily it is undesirable to prescribe more than three liters during each 24-hour period.

It may be well to mention at this point the possible advantages of using invert sugar, i.e., equal parts of fructose (levulose) and glucose, rather than glucose alone. It has been shown that the loss of sugar in urine with such mixtures is greatly reduced below those characteristically present with glucose solutions, even though high infusion rates are employed in administering the former. This desirable feature is attributable in part to the more rapid phosphorylation and glycogenation of the levulose and the accelerating effect of the latter sugar on the catabolism of glucose. Also the tubular reabsorption of the individual sugars is nonadditive and hence spillage does not occur (10a-d).

## VI. Treatment of Sodium and Chloride Deficits

In patients who have developed deficits of body sodium treatment should be directed toward: a) the interruption of the processes responsible for the depletion, b) the cancellation of the incurred deficits, and c) the provision of the daily needs.

It is obvious that success in achieving the first of these goals will depend upon the disease process. Thus it often is easy to interrupt gastrointestinal obstruction, to eliminate the excessive use of mercurial diuretics, to stop sodium losses in diabetic coma, or to replace the salt-retaining steroids which are lacking in adrenocortical insufficiency. On the other hand it is impossible to exert any immediate influence upon the sodium wastage of renal tubular disease. It is immediately apparent that the degree to which causative factors leading to sodium and to chloride depletion can be eliminated will influence the volume and the composition of fluid therapy.

The cancellation of the incurred deficits necessitates the administration of sodium and chloride solutions. Studies in animals indicate that the prompt replacement of these ions restores circulatory efficiency in great measure (figure 7-11), though not entirely (11a). The latter is true even when the entire deficit is made up, and reflects a small degree of residual

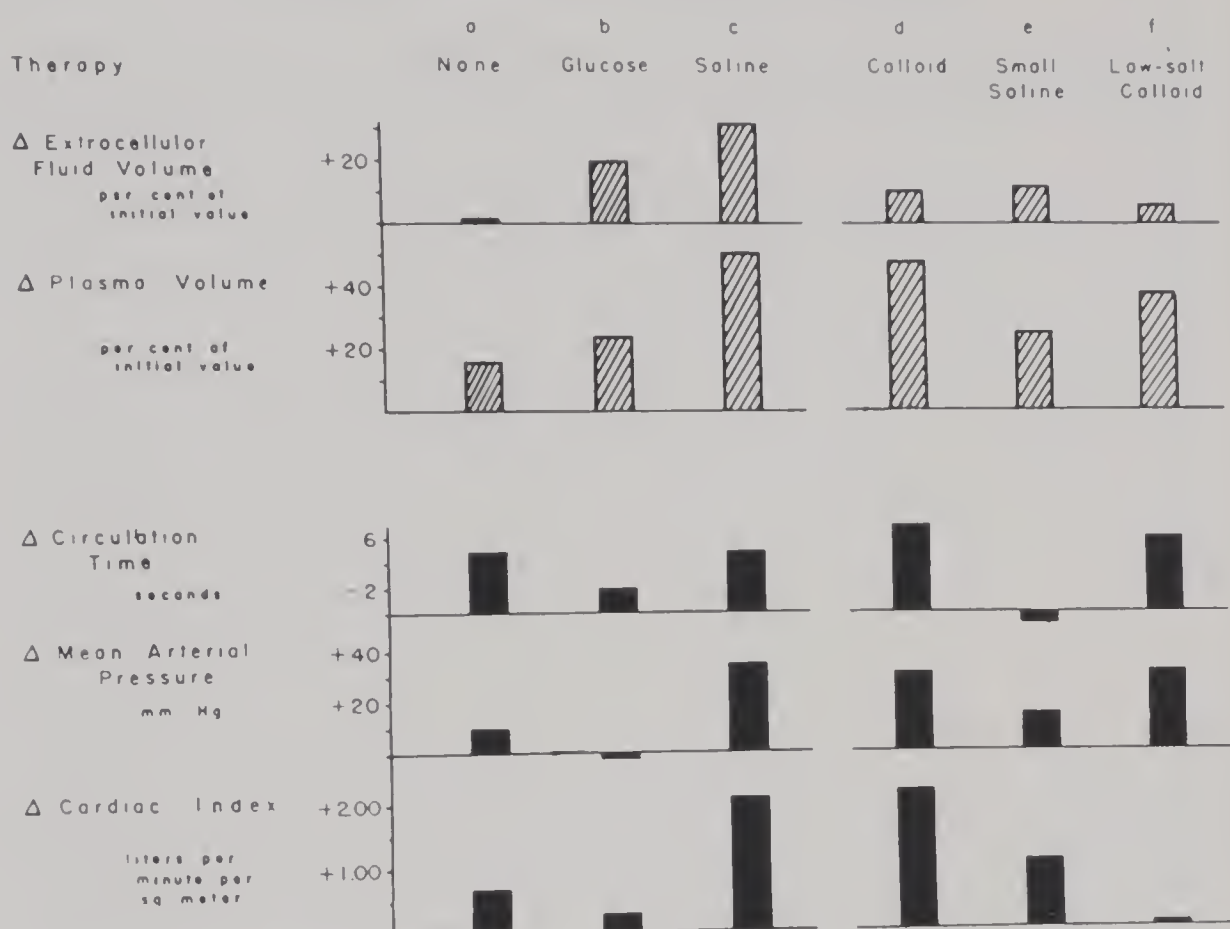


FIG. 7-11. SUMMARY OF THE MEAN EFFECTS OF TREATMENT WITH GLUCOSE, SALINE, AND COLLOIDAL SOLUTION ON THE CIRCULATORY FAILURE OF SODIUM-DEPLETED DOGS

Although all solutions produced some expansion of the plasma volume, only saline and colloids really restored the cardiac output. (From data of Winkler, Danowski, and Elkinton (11b).)

circulatory inefficiency which ultimately proves transient. Evidence is available indicating that the administration of colloidal solutions such as albumin or gelatin, concomitantly with the sodium chloride increases the degree of circulatory improvement (11b). Thus, small amounts of saline or of salt-free colloid are relatively ineffective in correcting salt depletion shock. On the other hand distinct improvement occurs when these same amounts of saline and salt-free colloids are given together. This is clearly evident from the data in figure 7-12. These data, and the finding that circulating protein disappears during salt depletion (5d), indicate that plasma, or other forms of colloid should be given in conjunction with salt replacement.

Recognition of the occurrence of salt depletion in diabetic coma, Addison's disease, vomiting, and diarrhea has been responsible for a distinct advance in the therapy of these conditions. The prompt administration of saline as well as colloid solution such as blood plasma or plasma substitutes

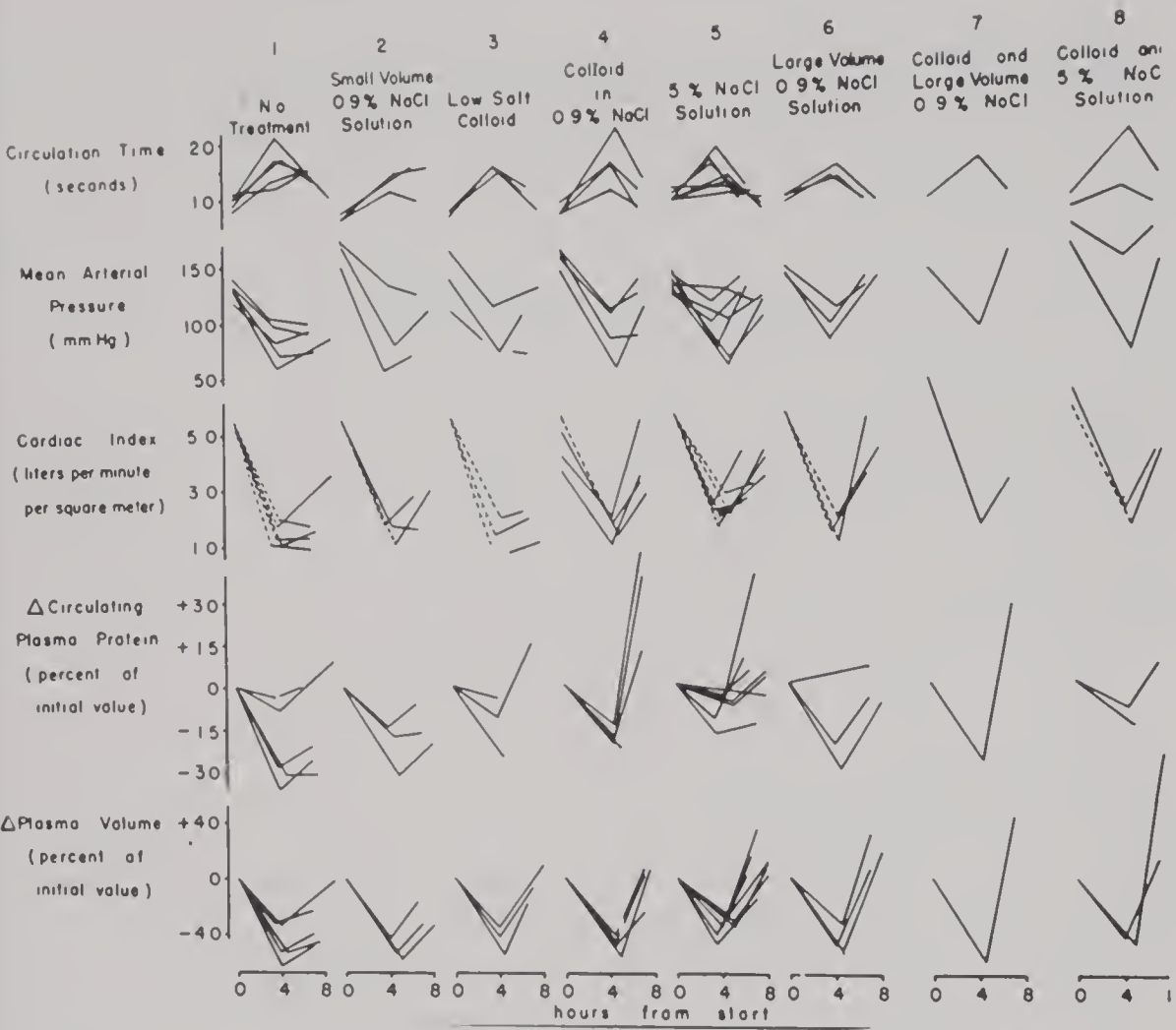


FIG. 7-12. EFFECTS OF TREATMENT OF SALT DEPLETION SHOCK WITH SOLUTIONS OF SALINE AND OF COLLOID

Salt depletion was induced between the first and second points (0 and 3 to 5 hours). Immediately after the second point an infusion of one of the solutions indicated at the top of the chart was administered. It is obvious that the combination of a small amount of saline and of colloid (column 4) produced circulatory improvement in the cardiac index (cardiac output in liters/minute/square meter) not seen with either above (columns 2 and 3). This points to an additive effect of saline and of colloid in the restoration of the circulatory collapse produced by sodium depletion. (From Winkler *et al* (11b).)

has contributed to the improvement in the mortality figures. Even though noncolloid solutions may at times suffice, experimental and clinical data indicate that the use of plasma volume expanders provides a needed margin of safety. Usually 0.9 per cent saline is used in treating salt depletion; it is administered in quantities sufficient to restore the concentrations and the total amounts of sodium and chloride to normal. In serious clinical situations two to five per cent, i.e., hypertonic saline solutions may be employed. It should be remembered that experience with these more concentrated solutions is limited and particular care must be taken to avoid



overtreatment and hypertonicity. Finally, in patients with limitations of kidney function it may prove necessary to use preparations which contain less chloride than sodium, i. e., of the type of Ringer's lactate, to prevent hyperchloremic acidosis.

Insofar as the daily needs for sodium chloride are concerned, our previous discussions of the body regulatory mechanisms in chapter 5 have indicated that there are none, *provided adrenocortical function is adequate and extrarenal losses of sodium and chloride do not occur* via the skin, gastrointestinal tract, etc. A small amount of salt, i.e., several grams, can be given as a margin of safety when water intake is adequate in patients without edema and with good renal function. Larger amounts should be given only when deficits are to be replaced, when extrarenal losses are large, or when renal sodium conservation is inadequate. Otherwise the high renal solute load may further aggravate the dehydration (2c).

### VII. Treatment of Potassium Deficits

It has already been pointed out that deficits of potassium in diarrhea, diabetic coma, renal disease, etc., can be masked by dehydration which converts the expected hypokalemia to normal or elevated levels of potassium. However, as replacement with potassium-free fluids is instituted, the patients show a drop in potassium levels which may reach abnormally low concentrations. Some of them will show the weakness, paralysis, and electrocardiographic changes which may occur with hypokalemia. From the viewpoint of survival these are of far less importance than the simultaneously present deficiencies of cell potassium. Function and morphology are adversely affected and death may result from potassium depletion even though the therapy in every other respect has been adequate.

The classification of hypokalemia into the three categories presented in section III of this chapter simplifies the prophylactic and therapeutic approach. Dilution hypokalemia is to be avoided in oliguric patients by limiting water administration to maintenance requirements. The drop in potassium which occurs with transfers of potassium into cells is clinically unimportant save that in periodic paralysis it should be prevented or treated by administration of several grams of potassium salts by mouth at appropriate intervals. In patients with deficits of cellular and extracellular potassium the underlying cause should be eradicated, if possible. Potassium salts are then given if the patient's condition is too grave to warrant reliance upon gradual replenishment from dietary sources.

The potassium should be given as early in the treatment as possible with due regard for the toxic effects of the ion if renal function is inadequate or if it is administered in excess (see chapter 9). It may be given as potassium chloride or as a buffered phosphate salt as indicated in chapter 24. Balance

studies indicate that as much as two hundred to four hundred milliequivalents of potassium may be retained during recovery (12a, b). It should be kept in mind that with the resumption of a general diet the potassium will be present in the food and supplementation is usually not necessary. Examples of potassium therapy are shown in figures 3-15, 11-9, 15-8, 15-9, 16-1, and 22-1.

### VIII. Deficits of Other Body Constituents

The emphasis upon the water, sodium, and potassium changes in this chapter should not be taken to mean that other important deficits are not present. Our knowledge concerning other body fluid constituents is accumulating gradually and rational programs in the future will have to provide for deficiencies of such components. Thus phosphate is already included in the therapy of conditions in which deficits of this element develop. On similar or on more precise grounds calcium, magnesium and other electrolytes may have to be supplied.

**SUMMARY:** The incurrence of deficits of body water in disease states without accompanying losses of electrolytes produces an increase in the concentration of solutes, disturbances in central nervous system function, and some deterioration of circulatory efficiency. On the other hand losses of sodium without proportionate deficits of water result in a decrease in solute concentration and in circulatory collapse. Potassium deficits produce variable alterations in the electrocardiogram, in muscle strength, in gastrointestinal motility, and in the morphologic integrity of cardiac and skeletal musculature. These physiologic effects of deficits of water and the chief electrolytes make replacement imperative.

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## *Chapter 8*

### **COMMON DENOMINATORS IN DISEASE STATES RESULTING IN AN EXCESS OF WATER OR ELECTROLYTES AND THEIR PHYSIOLOGIC SIGNIFICANCE**

In earlier chapters it has been indicated that, despite wide variations in intake, regulatory mechanisms maintain water, sodium, chloride and potassium within definite limits with respect to concentrations and total amounts in the various compartments. It naturally follows that these constituents can become overabundant only when the intake or input into the body or into its particular compartments exceeds the capacities of the regulatory mechanisms or when these mechanisms no longer operate normally.

The resultant alterations in any one of the components of the body fluids may or may not be accompanied by changes in the others. Hence in the paragraphs which follow excesses of body water will be discussed as they occur in subjects with normal, decreased, or increased sodium and chloride stores. Subsequently, excesses of sodium or of potassium, present in patients with intact, increased or decreased total body water will be described.

#### **I. Excesses of Water in Subjects with Essentially Intact Regulatory Mechanisms**

When renal and adrenocortical functions are intact it is impossible to take enough water by mouth to produce a persistent and positive net balance of water. Following a short lag period the kidneys can excrete water as fast as the surfeit limits will permit the taking of copious amounts of water. This is true even when the intake capacity is raised, as it is in some mentally disturbed patients, up to the point where the net water exchanges equal in magnitude those seen in diabetes insipidus. It is theoretically possible to overwhelm this capacity of normal kidneys for excreting water by sustained

infusion of fluids at rates in excess of maximal renal water output, i.e., higher than 13 cc. per minute (1a). This particular inadvertence has been reported (1b, c). It is of interest that in animal studies the resultant massive diuresis sweeps out small amounts of electrolyte and that this becomes manifest by a net loss of weight with little change in electrolyte levels.

## II. Water Excesses in Disease States

### A. *Water Intoxication with Electrolytes Intact*

Any process which interferes with the normal participation of the kidneys in the disposal of such extra water loads may, if the intake is more than adequate, result in water retention. This is encountered most often in patients with oliguria or anuria, due to acute tubular necrosis. Under such circumstances aqueous solutions of glucose are too often infused in the hope of inducing a renal output. If such water loads exceed the body output of water via insensible perspiration, a net gain in total water, cellular and extracellular, results since water freely traverses the cell boundary in response to changes in osmotic pressure. This dilutes the concentration of sodium and potassium both inside and outside of cells (see figs. 12-5 and 12-6). Under such circumstances a condition of water intoxication develops, with body solute stores essentially intact. Such excesses of water can produce abdominal and calf cramps and may produce convulsions (1d-j), but do not particularly affect the circulation (fig. 8-1).

Excesses of water develop however far more often in conjunction with decreased or increased stores and levels of sodium and chloride.

### B. *Water Excess in Combination with Electrolyte Depletion*

It has been pointed out in chapter 6 that a number of clinical situations can result in deficits of the chief extracellular electrolytes. Thus losses in vomitus, diarrheal stools, gastrointestinal drainage, sweat, or urine in the absence of adequate replacement via intake or input inevitably result in depletion of extracellular electrolytes. If such negative balances are not recognized, replacement fluids by mouth or via needle are apt to consist of aqueous solutions of glucose. If the net effect of such infusions maintains body water volume within normal limits, the patient is in a state of "pure" sodium and chloride depletion. If, however, the glucose solutions produce a net gain of water, a double distortion of body fluids develops as water excess or water intoxication is superimposed upon salt depletion. This means, of course, that the hypotonicity which characterizes pure salt depletion is further increased. These types of water excess are encountered in patients with upper gastrointestinal obstruction, diabetic acidosis, salt wasting renal disease, adrenocortical deficiency or any disorder in which

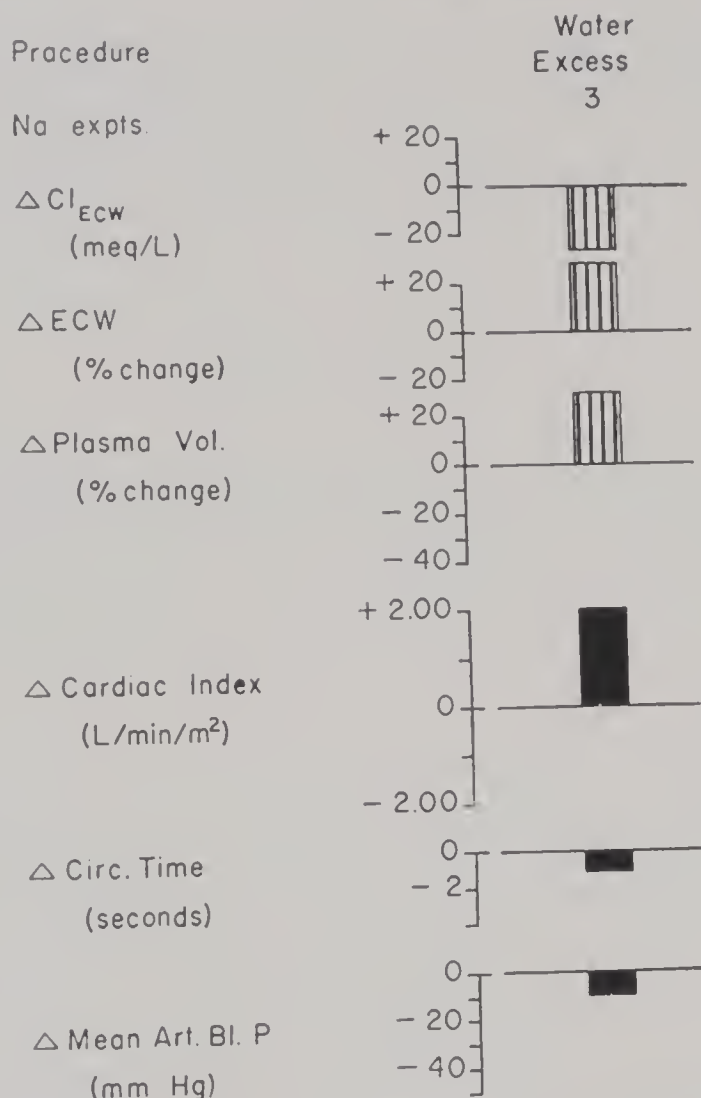


FIG. 8-1. CHANGES IN CIRCULATORY DYNAMICS IN HYPOTONICITY PRODUCED BY EXCESSES OF BODY WATER

Each column represents the mean value for the number of experiments indicated. The changes shown were produced in animals with normal body fluids. It is evident that a decrease in concentration alone produced by five per cent glucose in water has little if any deleterious effect upon the circulation. (Elkinton *et al* (2a).)

body fluid losses are replaced by solutions which do not contain the needed electrolytes.

The physiologic significance of these combined changes is clearly illustrated by the administration of glucose solutions to salt depleted animals (2a). Though cardiovascular function may improve, as shown in figure 7-5, this is transient if it does occur (see also fig. 24-1). In addition such animals are particularly prone to develop the convulsions of water intoxication. In clinical situations the same risks exist.

### C. Excess of Water and of Extracellular Electrolytes

When excesses of sodium and chloride develop, the tonicity of body fluids remains normal if just sufficient water is retained for this purpose;



additional water produces hypotonicity and less results in hypertonicity. The detailed factors which lead to such alterations, the disease entities in which they occur and their effects are discussed in later sections and chapters. At this point the net results of excessive body water can be summarized by saying that such increments always lower the tonicity of body fluids. *Thus hypotonicity is produced in subjects with intact salt stores, and aggravated in patients with salt depletion*; water retention reduces the tonicity of patients with excessive sodium and chloride stores toward, to, or below normal. Again it should be emphasized that an identical change in osmolar concentration, i.e., relative or absolute hypotonicity, must develop in both the cellular and extracellular compartments. Whether or not such changes prove beneficial depends in the last analysis upon whether the composition and volume of body fluids are thereby restored to normal or further distorted.

### III. Excesses of Sodium and Chloride in Subjects with Intact Regulatory Mechanisms

#### A. Physiologic "Excess" of Sodium and Chloride in Health

The ease with which sodium retention occurs even in healthy individuals is to be contrasted with the difficulty of producing water excesses in the same group of subjects. As a matter of fact, it might even be justifiable to look upon the sodium and chloride stores as being, in a sense, somewhat in excess under normal circumstances. This view is supported in part by recollection of the fact that the sodium excretion occurring during any particular day represents the excessive intake of the antecedent day or days, and that perhaps the true baseline with respect to the fundamental or essential sodium and chloride stores is that which develops after rigid sodium and chloride restriction has been imposed. Irrespective of whether one does or does not subscribe to such a view, the fact remains that ordinary diets contain sodium and chloride in amounts larger than are necessary for ordinary maintenance purposes.

This large intake of these two ions can quickly produce retention as a result of interference with the renal-adrenocortical-pituitary-hypothalamic facilitation of sodium and water output. Thus in many healthy women the alterations in the exchanges of sodium and water under the presumed influence of adrenocortical type steroids during the menstrual cycle are enough to produce clinically evident edema. The same sequence of events may occur as a result of certain combinations of intake and posture (2b).

### IV. Sodium and Chloride Excesses and Edema in Disease States

Disease processes or factors which involve the kidney, the adrenal cortex, and the higher centers may interfere with these regulatory mechanisms and produce retention of ingested or administered salt.

### *A. Salt Retention and Edema in Renal Disease, Congestive Failure, Cirrhosis and Toxemia*

The commonest causes of salt retention are those related to organic or functional impairment of the kidneys. Thus it has long been recognized that, as a group, patients with renal disease are apt to retain sodium and, in turn chloride and water, and thereby develop edema. This is true in the acute, subacute or chronic forms, though one must hasten to add that edema need not be present in one or all these phases. When edema does develop, it reflects a diminished renal excretory capacity which is, directly or indirectly, related to the nephritic component. The phrase "directly or indirectly" is used to emphasize the fact that in acute nephritis congestive heart failure may play a role in sodium retention apart from any specific kidney disease. These and other pertinent renal aspects of sodium and water metabolism involving the renal excretory apparatus are discussed in chapter 12.

Congestive heart failure of any type is associated with a diminished ability to excrete sodium. This fact has been known for at least 50 years (2c). It is the basis for many of the clinical manifestations in this entity and provides the basic rationale for a number of treatment programs. Since the subject is covered in detail in chapter 13, at this point it is sufficient to state that the retention of sodium is usually associated with diminished glomerular filtration, increased tubular reabsorption, or both.

Similar incapacity to dispose of extra salt is encountered in patients with cirrhosis and ascites (chapter 14) and in toxemia of pregnancy. In some of these patients evidence is available indicating that glomerulo-tubular imbalance is a factor.

In practically all these clinical conditions the possible participation of excessive adrenocortical activity in the salt retention has been advanced. This is a logical suggestion in view of the fact that adrenocortical steroids or related compounds do produce excessive tubular reabsorption of sodium and chloride, and in some of these disease states evidences of hyperadrenocorticism have been encountered. In all these entities sodium retention results from an intake in excess of excretion. The positive net balances of sodium and chloride are accompanied by a retention of water. Since sodium and chloride are predominantly extracellular ions, that portion of the body fluid expands. Some sodium and chloride and water do enter cells. Initially, however, such retentions of sodium, chloride, and water tend to occur chiefly in the extracellular space in the proportions in which these constituents are normally present in body fluids. This is the ordinary uncomplicated view of edema. Such edema, as it progresses, produces an increase in body weight, distension of viscera, subcutaneous swelling, accumulations of fluid in body cavities, dyspnea, and orthopnea.



*B. Edema: the Broad View*

Discussion of positive salt balances in clinical situations inevitably necessitates particular attention to the state of the body water stores. This can be illustrated by referring to patients who receive sodium in excess of their excretory ability, together with varying amounts of water. If the concomitant input of water is just sufficient to maintain water levels intact by replacing insensible and other losses, hypertonicity develops because the total amount of sodium and then of chloride has been raised without a proportionate increase in water. In hypertonicity of this type, as in the hypertonicity of dehydration described in chapter 6, mental confusion and disturbed judgment also appear. This is presumably a manifestation of dehydration of the central nervous system occurring in the presence of a hypertonic extracellular edema (2d-f).

On the other hand, if water is given in excess of replacement needs and is retained along with the sodium and chloride, an expansion of both the salt and water stores will occur with resultant edema.

Finally, if water is given and retained in excess of the net balances of sodium, then the body fluids expand and become hypotonic as a whole. In these patients muscle and abdominal cramps and convulsions can develop as they do in subjects with hypotonicity and intact or lowered stores of extracellular electrolytes.

The physiologic effects of these changes can be summarized by saying that edema, occult or manifest, may be and usually is present in all three of these combinations. Hence the usual view of edema must be broadened to indicate that expansions of extracellular fluid can be accompanied by increased or decreased concentrations of sodium and therefore by relative or absolute decreases or increases in the volumes of cell water, respectively. The problem is further complicated when it is recalled that exchanges of cellular ions may also be involved (see fig. 3-12 and chapter 13).

## **V. Excesses of Potassium in Subjects with Intact Regulatory Mechanisms**

It has been pointed out earlier (chapter 5) that studies of the distribution of administered potassium support the view that the cells of the body as a whole or certain tissues serve as a temporary storehouse for this element when it is ingested or injected at a rate in excess of the organism's ability to utilize or to excrete this element (3a-c). The excess is then gradually released to the extracellular fluid and excreted via the renal or extrarenal routes. If the rate of administration is excessive, and usually this can only occur via the venous route, extracellular concentrations and amounts will rise (4).



## VI. Excesses of Potassium in Disease States

As in the case of sodium, the extreme importance of the concomitant water balances upon the levels of potassium in the body has to be stressed. It is obvious that dehydration will increase the concentrations of this ion irrespective of the absolute amounts. Hence the simple presence of hyperkalemia does not mean that total stores are increased.

### A. Increments in Cellular or Extracellular Potassium

**Total** body potassium, i.e., cellular and extracellular, increases in renal disease, in adrenocortical insufficiency or in any clinical circumstance in which excretion cannot keep up with intake or input.

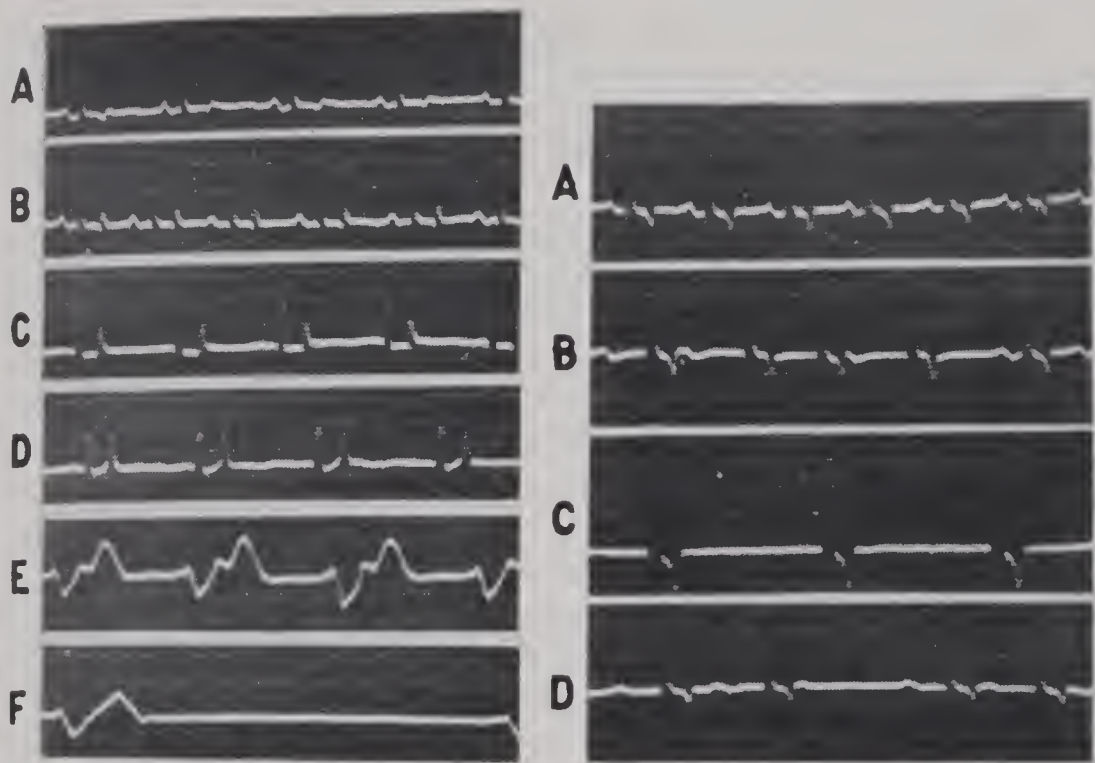
**Cellular** potassium increases at the expense of extracellular potassium in only one disease entity, familial periodic paralysis, though insulin or glucose therapy, glycogen formation, testosterone injection and a number of other factors can also produce transfers into cells. These are depicted in figure 7-6 which shows processes known to result in a net movement of potassium into cells.

**Extracellular** fluid receives increments of cell potassium as a consequence of anoxia, impending death, any interference with the metabolic processes which keep this element predominantly in cells, dehydration, muscle contraction or deglycogenation of the liver. This is illustrated in figure 7-7. However, adequate regulatory mechanisms readily dispose of the extra potassium via the usual excretory route and hence persistent increases in extracellular potassium usually indicate impairment of excretion. This occurs most often in anuric or oliguric subjects as in those with lower nephron nephrosis, diarrhea, diabetic coma, etc. (5a-d). (See fig. 9-9 and chapters 12 and 15.)

### B. Physiologic Concomitants of Potassium Excesses

Potassium excesses within cells produce no known harmful effects in and of themselves. This is in keeping with the concept that the cells can serve as a temporary storehouse for excesses of this ion (3c, 5b).

Neither do increases in the *total amount* of extracellular potassium produce any recognizable clinical or physiologic changes *if the levels of this electrolyte do not rise*. However, increases in the concentrations of extracellular potassium, irrespective of whether total amounts are normal, low, or increased do alter myocardial, muscular or neuromuscular and neurologic function. Thus the electrocardiogram shows the changes taken from the classic report of Winkler, Hoff and Smith (6) illustrated in figure 8-2. Also, weakness or paralysis may occur and dysaesthesia can appear (7). In all these instances it must be pointed out that the conditioning effects of the states of cell potassium or of other body electrolytes have not been defined.



Concentration of potassium in the serum (millimols per liter) at which various electrocardiographic changes appear

EXPERI- MENT	INITIAL CONCENTRA- TION OF POTASSIUM	INCREASE IN AMPLITUDE OF T WAVE	DEPRESSION OF S-T SEGMENT	DISAPPEAR- ANCE OF P WAVE	INTRA VEN- TRICULAR BLOCK	CARDIAC ARREST (DEATH)	REAPPEAR- ANCE OF P WAVE
1	4.1	5.0	9.0	10.5	11.4	14.7	
2	3.8	7.2	7.8	10.2	10.2	15.8	
3	4.9	6.4	9.4	9.4	9.4		7.9
4	5.5	7.8	9.0	11.0	12.0	14.3	
5	4.5				10.0	15.8	

FIG. 8-2. CLASSIC REPORT OF ECG EFFECTS OF HYPERKALEMIA AND THEIR RELATION TO POTASSIUM LEVELS IN SERUM

Serial electrocardiograms on the left taken during intravenous injection of potassium chloride. A, control; B, increase in amplitude of T wave; C, S-T segment drops below isoelectric line, and P wave disappears; D, accentuation of previous changes; E, spreading and beginning disorganization of Q R S complex; F, complete disorganization of Q R S complex just prior to final arrest.

Serial electrocardiograms on the right showing the reversibility of electrocardiographic changes following intravenous injection of potassium chloride (expt. 3). A, normal; B, increase in amplitude of T waves; C, disappearance of P wave and drop of S T segment. At this point the injection was stopped. D shows the reappearance of the P waves, with complete heart block; also rise in S-T segment and decrease in amplitude of T wave.

(Taken, *in toto* from Winkler, Hoff and Smith (6))

This is of particular importance in view of the demonstrated fact that, in contrast to the animal studies cited above, there is a general rather than a strict parallelism between extracellular levels and the appearance of the electrocardiographic changes.

## VII. Body Fluid Disturbances Produced by Deficits or Excesses

Having discussed the common denominators which can result in deficits or excesses of body fluid components, we are now prepared to think of their effects in terms of the general types of body fluid disturbances which result. These include changes in volume, in concentration, in relative ion concentration, and in regional distribution, alone or in combination.

### A. Volume Disturbances

Disturbances in volume produced by deficits or excesses may involve each of the several phases of the body fluids. Pure volume disturbances are those which do not involve change in concentration of either total electrolytes or any specific electrolyte. In other words, the volume of solvent or water of the phase has changed as well as the amount of solute or solutes contained therein. This may be true for extracellular fluid as a whole, for plasma or interstitial fluid, or for intracellular fluid. Such changes are shown for the extracellular fluid in figure 8-3. As seen in the figure, it is implicit that if there is a water change in the phase and no change in concentration of the main cation sodium, there must be a change of sodium in the same direction as that of water. Similar diagrams could be drawn for the other phases just mentioned. Such volume disturbances of extracellular fluid are commonly seen in edema of congestive heart failure, in nephrosis, in water and salt

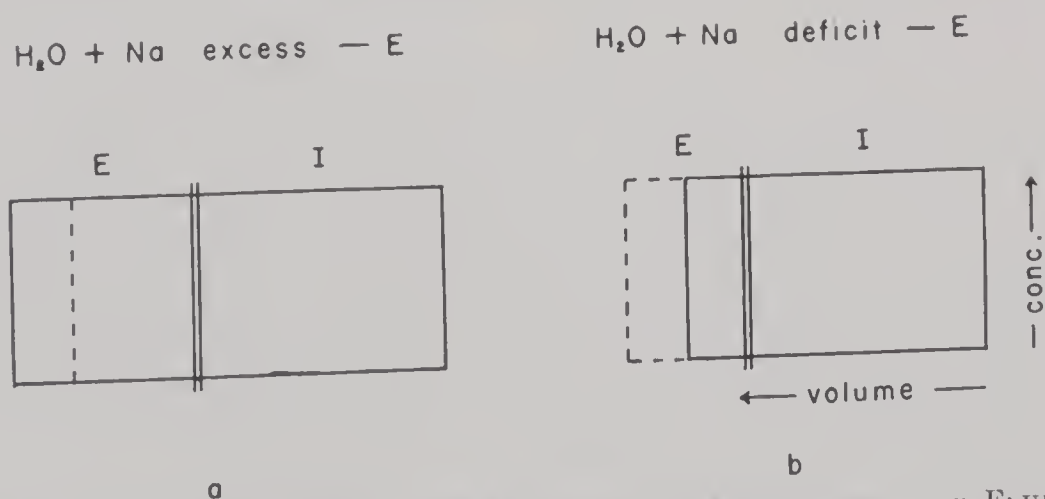


FIG. 8-3. DISTURBANCES IN THE VOLUME OF THE EXTRACELLULAR FLUID

Volume is plotted horizontally and concentrations are indicated along the ordinate in this and the next 3 figures.

The concentration of sodium remains unaltered in each instance because losses or gains of extracellular water and sodium occurred in the proportions in which they ordinarily exist in the body.



deficits as seen in patients who have had a gastrointestinal fluid loss or Addison's disease (see figs. 3-12, 3-15, 22-1).

### B. Concentration Disturbances

Under this heading are considered changes in the total electrolyte concentration of the body fluid produced by deficits or excesses. Since water is freely and rapidly diffusible between the extra- and intracellular phases, the concentration of the two phases is usually considered to be the same. This concentration may be measured by determining the total base concentration of serum or extracellular water. Since sodium is the major extracellular cation, the concentration of this ion gives an easily determined approximate concentration of the total extracellular and intracellular fluid electrolyte. As seen in figure 8-4 the main concentration disturbances are associated with either deficit or excess of solvent or deficit or excess of a solute, such as sodium. It is likewise evident from this drawing that concentration disturbances cannot be dissociated from volume disturbances.

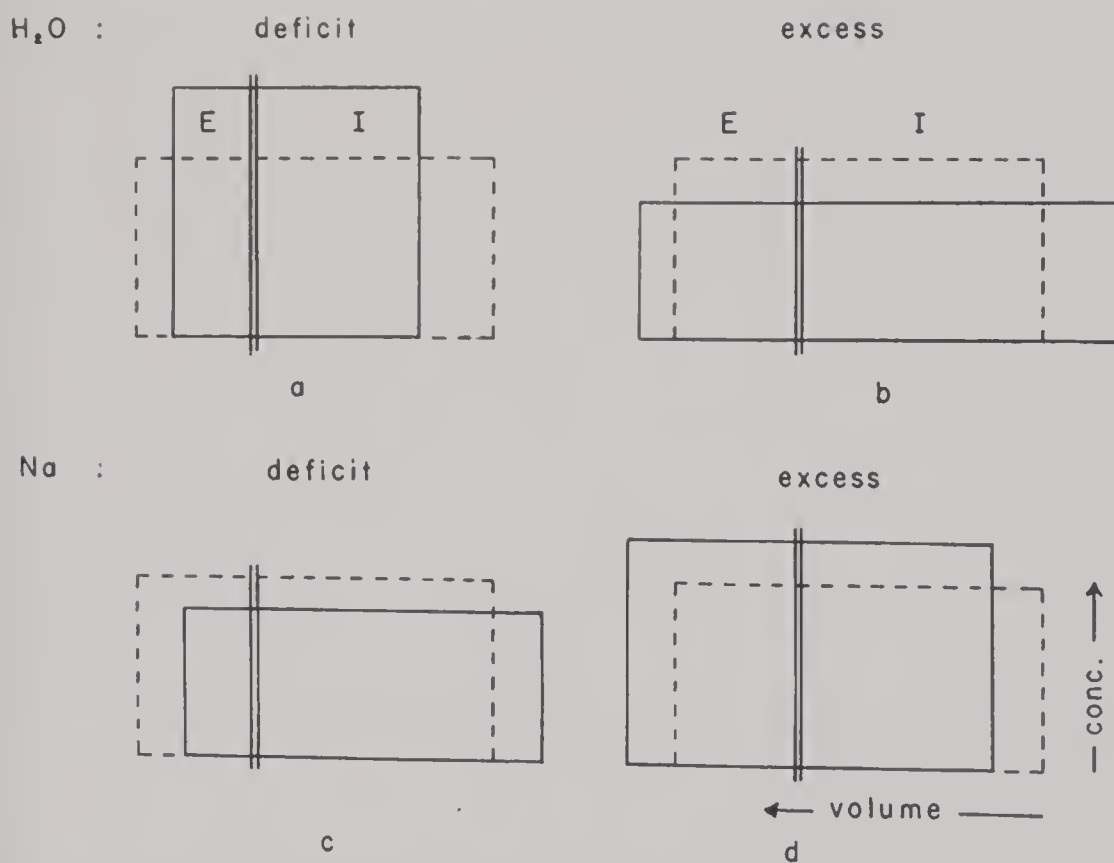


FIG. 8-4. DISTURBANCES IN CONCENTRATIONS AND IN VOLUME

Dotted lines identify normal volume and concentration relationships.

In the upper left-hand figure (a) dehydration (pure water deficit) has decreased the extra- and intracellular volumes and raised the electrolyte concentration. In c, sodium depletion has resulted in a lowering of sodium concentration and a shift of extracellular water into cells. In b, body fluids have been diluted and concentrations lowered by water excesses. In d, the administration of hypertonic saline has raised concentrations and drawn water out of cells.

Deficit of water as seen in water deprivation, dehydration and excessive sweating leads not only to an elevated electrolyte concentration in the body fluids, but also to diminution of both extracellular and intracellular fluid volumes. This happens because, as water is removed from the extracellular phase, intracellular water diffuses out into the extracellular space to maintain an equal electrolyte concentration (see figs. 2-6, 20-1).

Conversely, overloading of the body with water leads not only to a depression of the total electrolyte concentration, but also to an overexpansion of both fluid phases. This is most commonly seen in the anuric patient who receives large amounts of sodium-free water (see figs. 12-5, 12-6). It can also be produced experimentally by the injection of posterior pituitary antidiuretic hormone together with a water load (see chapter 19).

Changes in sodium or in the principal electrolytes of the extracellular fluid also produce secondary changes in volume as well as concentration. Sodium deficit in relation to water as produced experimentally by the removal of sodium through intraperitoneal lavage or as seen clinically in the patient who loses sodium containing gastrointestinal fluids, but replaces some of the water, leads not only to a lowering of the total electrolyte concentration, but also to a shift of water into the cells (see fig. 2-6).

The converse of this condition, the loading of the extracellular phase with hypertonic solutions of sodium, leads to an elevation of the total electrolyte concentration and a withdrawal of water from cells. This may be produced experimentally by the injection of hypertonic sodium-containing solutions or is seen in individuals who are cast away at sea and who drink large amounts of sea water (see fig. 2-8 and chapter 2).

Thus the determination of serum sodium or of total base in any given sick patient gives some clue as to the type of concentration disturbance present. In figure 8-4, only those disturbances in concentration and in volume which originate in the extracellular fluid have been shown. As pointed out in the first chapter, primary changes may take place within the intracellular phase as well. Thus it is quite possible that changes in the size and osmolarity of solutes within the cell, production of solutes such as protein, or formation of water during the oxidation of foodstuffs may also lead to disturbances in concentration and volume of the total body fluids (see fig. 1-9).

### *C. Relative Ion Disturbances*

So far disturbances have been presented involving only the total volumes of water and the total electrolyte concentrations of the several phases of the body fluids. Since the electrolytic pattern of each phase is made up of a large number of ions, it is quite possible that the concentration of some of these ions relative to each other may be changed as a consequence of excesses or deficits without any necessary alteration in either the total

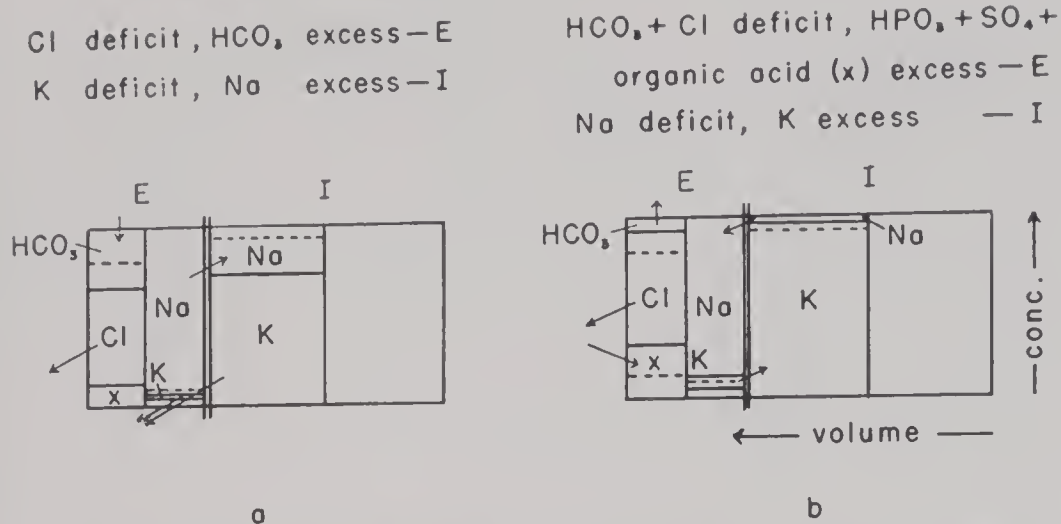


FIG. 8-5. DISTURBANCES IN RELATIVE IONIC CONCENTRATION

An attempt has been made to present orders of magnitude via a mirror image of a Gamble diagram superimposed upon the extracellular space (E) (as in fig. 3-6, c). The arrows point to internal and external transfers of electrolytes.

In A, hypochloremic alkalosis is shown in association with cell deficits of potassium; sodium has replaced some of the cell potassium. In B, a metabolic acidosis of the type which occurs in renal failure is shown with evidences of sodium deficit and potassium accumulation within cells.

electrolyte concentration or the total volume of the solvent water. Two such disturbances are shown in figure 8-5. On the left is presented the change in relative ion concentrations that might take place in a patient with severe vomiting and with the development of potassium deficiency. Chloride is usually lost from the extracellular fluid and replaced by bicarbonate. Potassium may leave the intracellular phase and sodium enter in its place without any change in volume or total concentration of electrolyte (see figs. 3-15, 22-1). Actually in this condition there are usually changes in volume as well but this is not necessarily so. Another example shown in the right half of figure 8-5 is that of a patient with severe renal insufficiency. As phosphates and sulfates and undetermined acids pile up in the extracellular fluid, bicarbonate ion is displaced (see fig. 12-5). Potassium may be retained as well in both extracellular and intracellular phases and there may be a shift of sodium from the cells outward. Again this conceivably might occur without any change in total volume of either phase, or of the total electrolyte concentration, and again some change in volume may take place. Thus, in any disturbance one has to consider the changes in relative ion concentrations as well as the other dimensions of disturbance in the body fluids.

#### D. Regional Distribution Disturbances

As indicated earlier, the body fluids are homogeneous solutions only to the extent that the mixing apparatus or the circulation is working well.



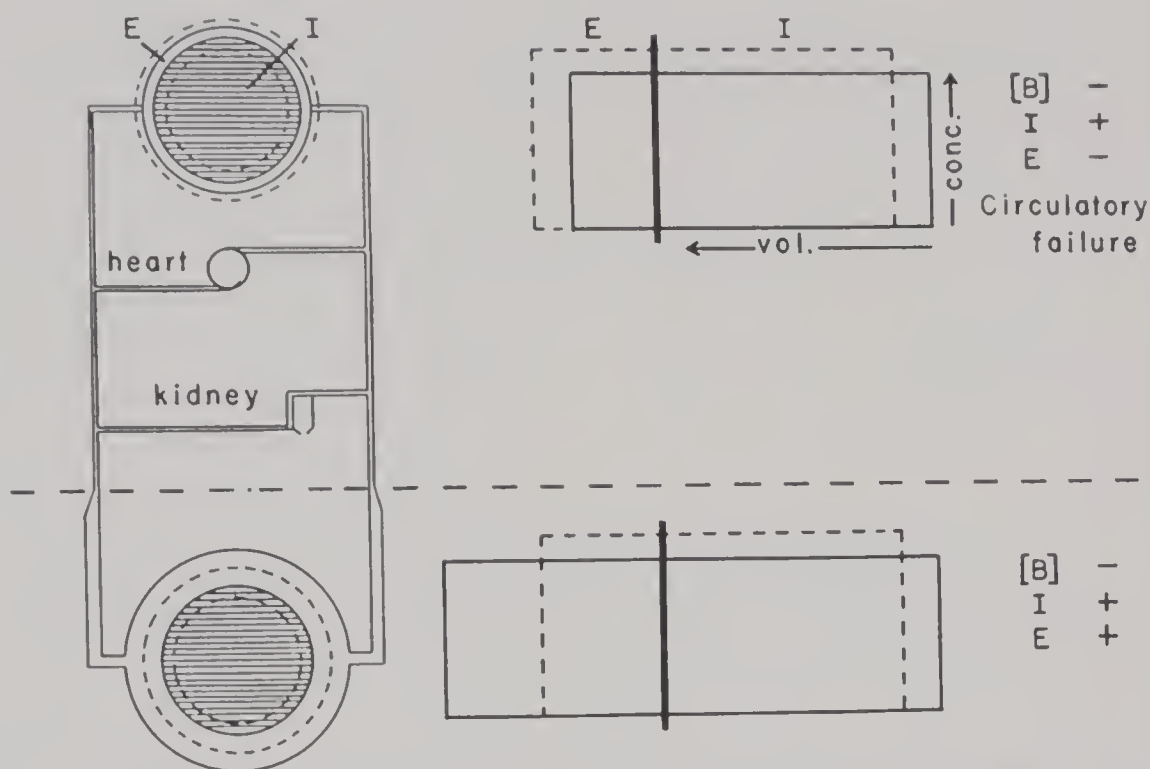


FIG. 8-6. DISTURBANCE IN REGIONAL DISTRIBUTION: DIAGRAM OF "SYSTEMIC" DEHYDRATION IN THE PRESENCE OF EDEMA

The dotted line represents volume and concentrations in health. In the upper portion of this figure low sodium syndrome ( $[B^+]I^-$ ) stemming from salt depletion is shown. In the lower portion low salt syndrome on the basis of excessive water retention is illustrated. These two figures emphasize the possibility of dehydration in the presence of an edema, (see fig. 1-11). (From Elkinton and Squires (8).)

Considering the fact that the four types of fluid movements between the three phase system of plasma, interstitial fluid, and intracellular fluid are working in many different parts of the body simultaneously in an integrated fashion, it is easy to understand how there may be differences in regional distribution of fluids in disease states characterized by deficits or excesses. Such a disparity in distribution as seen in certain types of the "low-salt syndrome" is illustrated in figure 8-6. Here the patient with congestive heart failure has an excess of sodium and water in the extracellular phase in certain parts of the body, usually dependent portions. However, following the prolonged use of low-salt diets and mercurial diuretics, such patients sometimes develop evidences of peripheral vascular collapse and renal insufficiency (see fig. 13-2). It would appear that although these patients have an excess of extracellular fluid and at times of plasma volume, the circulation through organs such as the kidney is less than adequate. Such differences in distribution obviously affect renal function and the ability of the circulation to move fluid from depots of excessive sodium and water to the excretory organ.

### *E. Mixed Disturbances*

As stated above, in most clinical situations where the body fluids are abnormal, the abnormalities consist of changes in more than one of these dimensions, i.e., excesses and deficits may be present at the same time. This concept is important because the physician in treating his patient must consider carefully which abnormality is the more important one to treat and whether he can treat more than one simultaneously. In analyzing the clinical problem, furthermore, it will be useful to consider what are the disturbances of volume, concentration, relative ion concentration, and regional distribution, and to assess the importance of the therapy of each in turn.

**SUMMARY:** As in the case of deficits, excesses may occur as common factors in various diseases and manifest themselves as, or in conjunction with, disturbances in volume, concentrations, or distribution, alone or in combination.

A more than transient increase in water without great change in solutes occurs with excessive intake or input of water in patients with oliguria and anuria. Such patients are particularly apt to develop generalized convulsions. Relative excesses of water may also occur in a more or less chronic form in patients with illnesses in which volume and concentration regulation is disturbed, as in congestive heart failure, cirrhosis, or chronic nephritis. Attempts to raise concentrations of solutes in such patients usually only induce thirst and increase edema.

Excesses of sodium may be present with unchanged, increased, or decreased concentrations of this ion, and occur when the circulatory, renal or regulatory mechanisms are disordered or overwhelmed. With increases in the total amount of sodium and of water, edema ensues; the tonicity of body fluids then depends on the retention of water relative to the retention of sodium. Pronounced elevations of sodium concentrations irrespective of their origin produce cellular dehydration, deterioration of cerebral function and even respiratory failure.

Body potassium stores increase when the input exceeds excretion. Undue increases in extracellular potassium alter the electrocardiogram and may affect sensation and motor strength, whereas rises in cell potassium appear to represent a mechanism for the safe storage of excesses of this electrolyte.

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## *Chapter 9*

### **THERAPY OF EXCESSES OF WATER OR OF THE CHIEF ELECTROLYTES**

Removal of excesses of body water or of the chief electrolytes in general presents more problems than those encountered in the replacement of deficits. Nonetheless the knowledge and the tools available to the clinician for this purpose are increasing. Their application is discussed in the sections which follow.

#### **I. Treatment of Water Excesses**

Lowering the volume of body water is relatively easy in the anuric patient who has been inadvertently overtreated with water. Simply withholding fluids will restore tonicity, as the insensible loss of water continues. Application of certain types of artificial kidneys as described in chapter 25 will also remove water, though at a limited rate (1a, b) (see fig. 25-7).

When such attempts to correct hypotonicity by decreasing body water are unsuccessful, the question of sodium chloride administration as a means of restoring normal tonicity should be raised, though with care and caution. This will be beneficial only in those patients in whom an element of salt depletion is present or in those with symptoms or signs of water intoxication, and may prove harmful in hypertension.

In other types of patients hypotonicity usually reflects the presence of disordered or reset volume and osmoreceptors. In such instances, occurring usually though not invariably in clinically edematous cirrhotic, nephritic, or congestive failure patients, attempts to raise concentrations to normal by dehydration or by salt administration provoke marked thirst and discomfort and, with the latter procedure, increase the edema. The hypotonicity promptly reappears as free access to water is again permitted. The best approach to the resolution of hypotonicity not attributable to salt depletion is to concentrate upon the primary site of the disease, whether it

be heart, kidney, or liver. Improvement in the function of the particular organ in the presence of adequate renal excretory ability is followed by automatic restoration of normal volume and concentration relationships. This problem is discussed in greater detail in the chapters dealing with these three organs.

## II. Treatment of Sodium and Chloride Excesses

A negative salt balance can be achieved by decreasing ingested or injected sodium and chloride, increasing renal and extrarenal losses of the electrolytes, or both. If the problem is one of prevention, then the achievement of an equilibrium between intake and loss becomes the goal.

### A. *Withdrawal of Dietary Salt*

The efficacy of such a procedure in any individual patient is dependent upon: *a)* the degree to which dietary sodium *is reduced*, and *b)* the degree to which dietary sodium *must be reduced* to achieve either equilibrium or negative balances of sodium. Not all clinical situations in which limitations of sodium intake are indicated necessitate the same *degree* of restriction. Thus, when sodium excesses and edema appear on the ordinary general diet, avoidance of foods obviously high in sodium content, such as preserved meats, together with elimination of salt in the preparation and serving of food may prove adequate. In such instances the daily intake of the ion is reduced only slightly and yet this difference is enough to tilt the sodium balance and to prevent further accumulation or to produce a diuresis. Unfortunately, too often such relatively slight reductions in dietary sodium do prove inadequate in controlling salt retention in congestive failure, cirrhosis, or the nephrotic syndrome. In such patients a careful selection of foodstuffs, together with the exclusion of sodium during their preparation and from basic items such as bread and butter will reduce the daily intake of this electrolyte down to as little as 300 or even 50 milligrams. Representative chemical analyses of foods for this purpose are readily available in a number of publications (2a, b), and will not be duplicated here. It may be helpful to remember however that old-fashioned cereals, fresh fruits, and vegetables have, in contrast to meats, fish, and milk, only traces of sodium. Almost all the sodium in milk can be removed by dialysis and hence sodium-free milk can be included in such restricted diets. Unfortunately, this is not possible with meat and fish. Finally, in many areas, particularly those in which water softeners are in operation, distilled or untreated water will have to be used to achieve this measure of restriction.

Sample low-salt diets containing 50 or 300 milligrams of sodium, i.e., two and 13 milliequivalents respectively, are given in the appendix. This regimen also provides 150 to 200 milliequivalents of potassium each day.



It is obvious from the attached estimates that these diets are adequate from the viewpoint of carbohydrate, fat, and protein. Extra iron and vitamins have to be supplied. Though such diets do not have the characteristic array of meat or fish, potato, and vegetable they are quite well received by children and can be made acceptable to almost all adult patients, if particular care is taken in their selection and preparation. This we have found to be true in treating large series of rheumatic fever patients, as well as children and adults hospitalized with renal disease (3a-c).

Prolonged dietary sodium restriction does, however, prove burdensome to many patients. In an attempt to increase dietary palatability salt substitutes have been devised. Most of these contain ammonium and potassium salts which impart some pungency to the diet but do not prove universally acceptable (4). The lithium salts employed for this purpose, however, had to be discontinued because of serious toxic reactions (5a-e). Furthermore, in patients with renal failure and its attendant trends toward acidosis and hyperkalemia ammonium and potassium ions are also contraindicated, even though the total daily intake may be quite small.

These limitations of sodium restricted diets have led to attempts to interfere with the absorption of ingested salt by a variety of means.

### *B. Removal of Gastrointestinal Sodium by Irrigation, by Dialysis or by Exchange Resins*

Since gastrointestinal secretions are known to contain large amounts of sodium, gastric or intestinal lavage, colonic irrigation, and catharsis have occasionally been employed in attempts to augment the excretion of this ion from the body. All of these procedures have been abandoned, largely because of their unpredictability and inefficiency. The artificial kidney, however, does serve as an effective modern day counterpart of these dialytic procedures. This is taken up in great detail in chapter 25.

The possibility of augmenting electrolyte excretion via the gastrointestinal tract has been re-explored with the availability of cation exchange resins which, in contrast to cathartics, alter stool composition in a somewhat more specific and generally predictable manner. These agents when taken by mouth ultimately bind positive charged electrolytes in the gastrointestinal secretions. Since they are indestructible and too large to be absorbed, they are excreted unchanged in the feces together with associated electrolytes.

**1. Chemical structure and properties of exchange resins.** Structurally, cation exchange resins consist of conglomerations of six carbon rings interlocked at various points by carbon linkages (fig. 9-1). In these molecules one or more of the hydrogen atoms on the benzene rings has been replaced by chemical groups such as the carboxyl or sulfonic ( $-\text{COOH}$  or  $-\text{SO}_3\text{H}$ ).

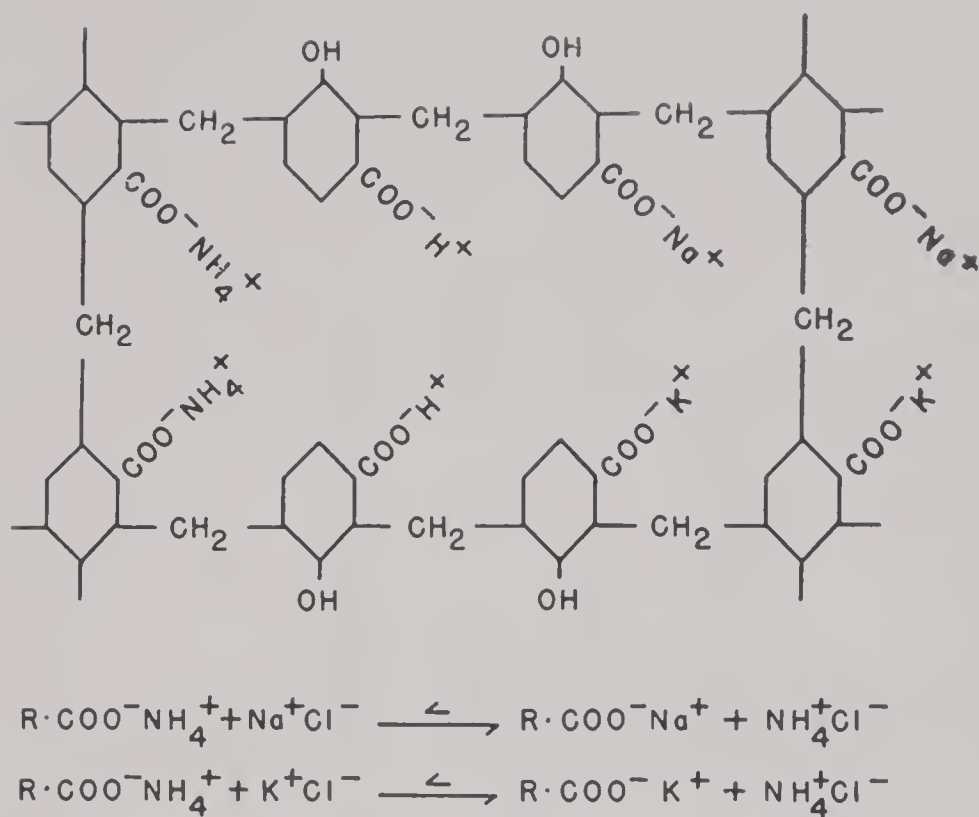


FIG. 9-1. CHEMICAL STRUCTURE OF A SEGMENT OF A CARBOXYLIC CATION EXCHANGE RESIN

The carboxylic side-chains ( $\text{COO}^-$ ) are shown with various cations attached: ammonium, hydrogen, sodium, and potassium. The reactions of the ammonium cycle resin with  $\text{NaCl}$  and  $\text{KCl}$  are indicated.

When the resin has reacted with acid, hydrogen ions occupy the terminal positions of the carboxyl or sulfonic groups; it is then said to be in the hydrogen form. The phrase "in the sodium form or cycle" applied to the exchanger indicates that the hydrogen ion has been supplanted by sodium. If it is displaced by potassium then it would be called the "potassium form" of the resin. The carboxylic resin differs from the sulfonic in that with the latter exchanges of the hydrogen ion for other cations can occur at lower pH values (6a-d). In liquid media, *in vitro* and in the gastrointestinal tract, the hydrogen ion of these two groups ionizes and can be exchanged for other cations such as sodium and potassium which are then excreted in feces. This is shown in figure 9-2.

These complex macromolecules can be described as huge anions with attached cations. Such polyelectrolytes possess a variable affinity for cations depending on the degree of their cross-linkage, the nature of the solvent, the characteristics of the individual cations such as the atomic weight, the radius of the unhydrated nucleus, the valence, and a host of other less well-defined factors. Under identical conditions, for example, the exchanger will preferentially bind larger amounts of potassium than of sodium, and more of a divalent cation such as calcium than of either potassium or sodium which are univalent. However this hierarchy of affinities for the different

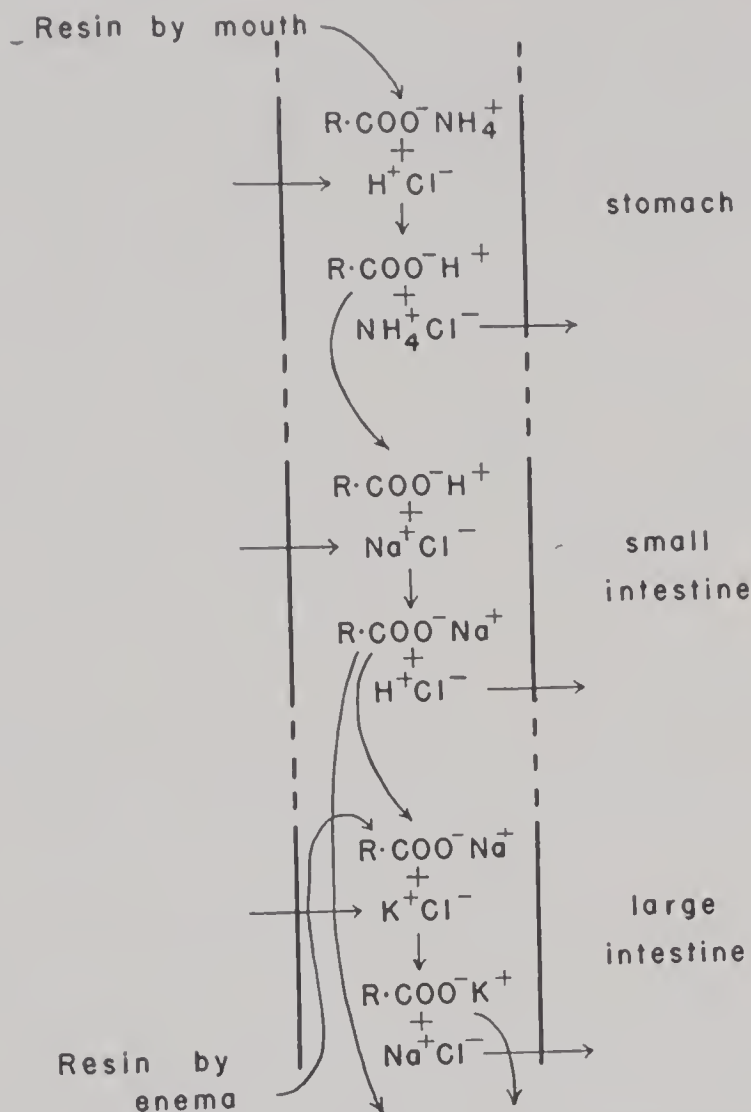


FIG. 9-2. THE PRINCIPAL REACTIONS OF CATION EXCHANGE RESIN IN THE GASTROINTESTINAL TRACT

Carboxylic resin in the ammonium cycle given by mouth exchanges for hydrogen in the stomach; hydrogen is then exchanged for sodium and potassium in the small and large intestines. Introduction by enema into the colon of resin in the sodium cycle as shown, or more commonly in the hydrogen or ammonium cycle, results in an exchange primarily for potassium. This is a useful technic in potassium intoxication. The resin also exchanges for calcium and magnesium but to a much smaller degree (9b).

cations yields to the electrolytes which predominate in the environment in which the resin is placed. Since sodium and potassium are the chief ions in the gut, the exchanger primarily affects their excretion (6a-d, 7).

At times anion exchange resins are used in conjunction with cation exchangers. This class of compounds is referred to as the alkylene polyamine exchangers. In some laboratories it has been found that the addition of a small amount of an anionic exchanger of this type minimizes the acidosis and increases the efficiency of cation exchange resins (8a-c).

**2. Resin effects in animal and in human control studies.** The



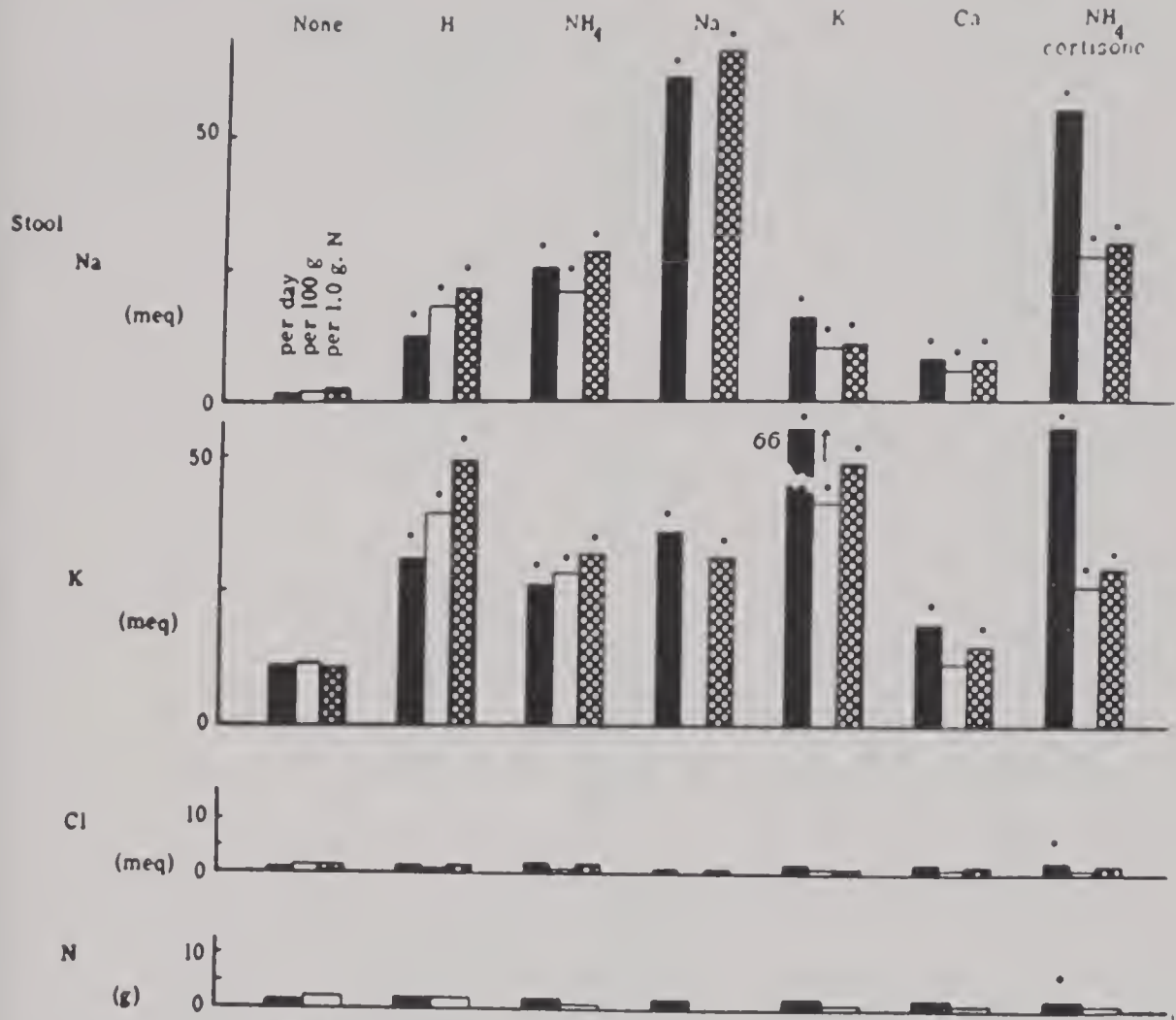


FIG. 9-3. FECAL ELECTROLYTES DURING CATION EXCHANGE RESIN THERAPY

The columns represent stool excretion of Na, K, Cl, and N per day, per 100 grams of wet stool, and per 1.0 gram of nitrogen during therapy indicated at the head of each group of columns. The chemical abbreviations indicate the form of the resin ingested, and the asterisks stand for values significantly different from the control column entitled "none." The column headed "NH<sub>4</sub> cortisone" indicates a patient receiving the NH<sub>4</sub> form of the resin together with cortisone. Stool excretion of sodium and of potassium increased to a variable degree irrespective of the particular form of the resin administered, or of cortisone therapy. Mean stool chloride and nitrogen values were not changed during the ingestion of any of the exchangers, but did increase slightly when cortisone was given during NH<sub>4</sub> form therapy in one patient. (From Greenman *et al* (9b).)

administration of certain but not all forms of carboxylic or sulfonic resins to dogs for several days in 20- to 40-gram amounts or to humans in 30- to 80-gram quantities alters the composition of feces, the body fluids, and urine (9a-c). If a resin precharged with hydrogen or ammonium ions is used, the stool output of sodium and of potassium rises (fig. 9-3); the released hydrogen or ammonium ions are absorbed and a metabolic acidosis results characterized by hyperchloremia and a lowered total serum CO<sub>2</sub> content (fig. 9-4); the urinary output of sodium and potassium decreases

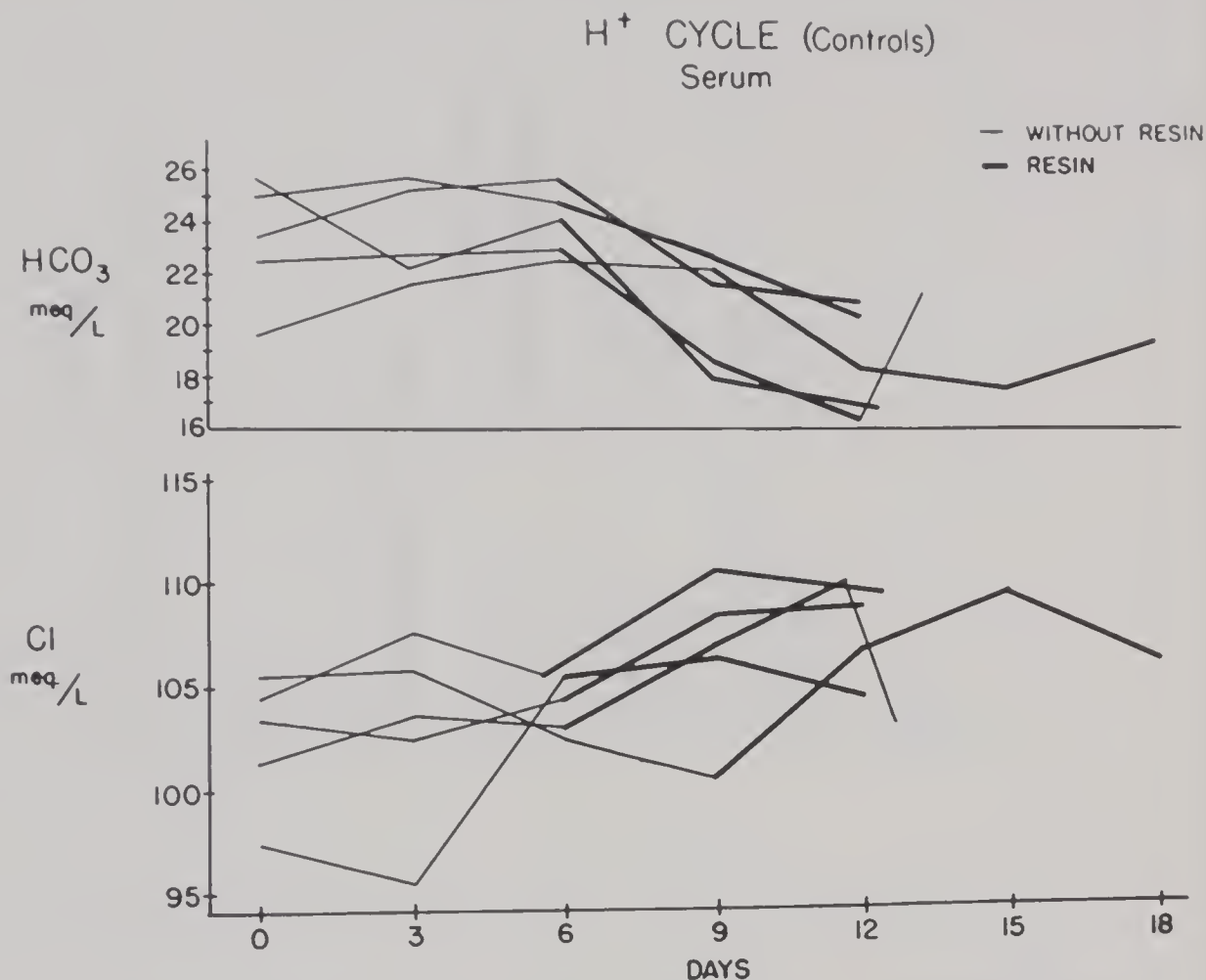


FIG. 9-4. SERUM  $HCO_3^-$  AND Cl DURING CATION EXCHANGE RESIN ADMINISTRATION

The administration of a carboxylic exchanger in the hydrogen cycle to hospitalized diabetic children produced hyperchloremia and acidosis (From Danowski *et al.*, (9d)).

(fig. 9-5) and, after several days, an increased renal production of ammonia and of the ammonium ion is evident. On the other hand the ingestion of an exchanger precharged with potassium eliminates the acidosis and leads to absorption of some of the potassium fed with the resin. Finally, the use of a resin to which calcium has been bound virtually deprives it of any of these effects, presumably because of its greater affinity for polyvalent cations. The resins which produce an acidosis, i.e., those precharged with  $H^+$  or  $NH_4^+$  are referred to as acidifying in type, while the others are called non-acidifying (9a-c).

The daily fecal output of sodium and potassium in patients on a variety of diets with and without a carboxylic exchanger in the hydrogen form is shown in table 9-I (10).

It is readily evident that the formed stool in man has more potassium than sodium. The resin significantly raises the output of both of these ions but in percentage terms the rise is greater in the case of sodium even though larger amounts of potassium are lost.

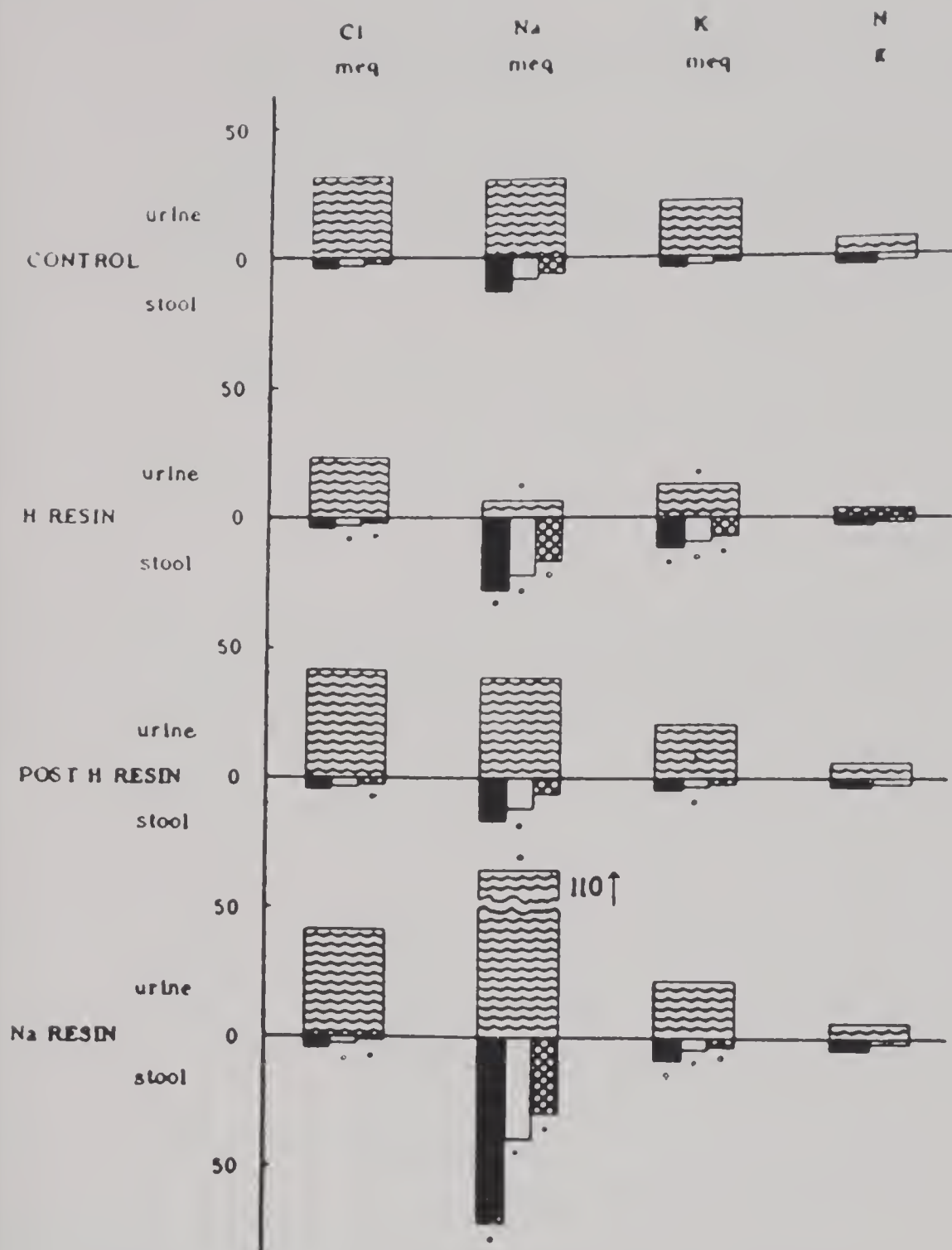


FIG. 9-5. DAILY EXCRETIONS OF ELECTROLYTES AND OF NITROGEN IN URINE AND IN STOOLS DURING CATION EXCHANGE RESIN THERAPY

Columns with horizontal waves depict daily urinary excretion of the constituent. The smaller columns below the horizontal lines are based on stool data. Black columns refer to mean per day values, open columns indicate excretion per 100 grams of stool and the crosshatching identifies the electrolyte:nitrogen ratio. The small circles indicate that the change in the mean from the control is statistically significant.

Ingestion of the  $H^+$  form of the resin increased the stool excretion of potassium and of sodium above control values. This was accompanied by decreased urinary output of these electrolytes. The sodium form of the resin also raised the stool potassium and sodium. Urinary potassium in these experiments, however, did not decrease below control values. Urinary sodium on the other hand rose markedly. The changes in stool chloride were present only irregularly and were of small magnitude and no significant alterations occurred in urine chloride. Nitrogen excretion was not altered. (From Danowski *et al* (9a).)



TABLE 9-I.

EFFECTS OF A CARBOXYLIC CATION EXCHANGER (RCOOH) UPON THE COMPOSITION OF FECES*				
Specimens	Resin g/d	Excretion per day (mEq)		
		Na <sup>+</sup>		K <sup>+</sup>
		Mean	± S.D.	Mean ± S.D.
23	none	3.9	± 4.5	9.7 ± 4.8
26	34	20.9	± 25.4	30.6 ± 22.2

\* Taken from Danowski and Greenman (10)

TABLE 9-II.

EFFECTS OF A CARBOXYLIC CATION EXCHANGER PRECHARGED WITH VARIOUS CATIONS UPON THE FECAL EXCRETION OF NA AND K*				
Form of carboxylic resin	Specimens	Excretion of Na + K in feces/gm. of resin		
		Na (mEq.)		K (mEq.)
		Mean	± S.D.	Mean ± S.D.
H <sup>+</sup>	26	0.6	± 0.7	1.1 ± 0.9
NH <sub>4</sub> <sup>+</sup>	8	0.6	± 0.4	0.7 ± 0.3
K <sup>+</sup>	6	0.4	± 0.5	1.4 ± 0.7
Ca <sup>++</sup>	9	0.2	± 0.1	0.5 ± 0.3
Na <sup>+</sup>	3	1.5	± 0.6	0.9 ± 0.5

\* Taken from Danowski and Greenman (10)

In table 9-II the relative effectiveness of the various forms of a carboxylic exchanger are shown (10).

It is immediately obvious that the two acidifying forms of the resin are of equal efficiency in augmenting sodium output and that on the average a 60-gram intake of resin should remove about 36 milliequivalents of sodium. This is equal to a dietary intake of some four grams of sodium expressed as sodium chloride.

An interesting observation in patients with Addison's disease sheds some light upon mechanisms which limit the amounts of sodium removed. In adrenocortical insufficiency these same resins remove four or five times as much sodium per gram of resin (11), indicating that this endocrine normally facilitates the reabsorption of sodium from the gut just as it does in the kidney. In line with this, adrenocortical hyperactivity has been advanced as a partial explanation for decreased efficiency of the exchangers in certain edematous patients (12a-c).

There is no evidence that the sulfonic types exchangers are any more efficient or that any large net gain in efficiency results from the simultaneous use of an anion and cation exchanger (10, 13). The latter combination probably does minimize acidosis and hyperchloremia, but unfortunately still does not permit free use of the exchangers in patients with renal failure.

**3. The clinical effects of exchange resins.** Most patients can tolerate the resins for prolonged periods of time though gastrointestinal distress such as a sense of fullness, eructation, constipation and, occasionally, diarrhea may develop (9d, 14a, b).

These agents have proved useful in controlling the edema of congestive failure, nephrosis, cirrhosis, as well as in sodium restriction for hypertensive vascular disease or toxemia of pregnancy provided that some dietary restriction is practiced at the same time (14b, 15a-k). Usually an 80:20 mixture of the H:K forms is used for this purpose to minimize the possibility of potassium depletion. It appears best to use the resins intermittently, i.e., four days on and three days off, since this allows periodic disappearance of the acidosis which develops and permits absorption of calcium, iron, and other food essentials unhampered by the presence of resins (see figs. 13-4 to 13-8).

Several warnings are in order: the combination of sodium restriction, resin therapy, and losses of body fluids as in urine, diarrhea, sweating, etc. can result in sodium or potassium depletion (14b); the acidifying exchangers should be used with caution in renal failure, but this also applies to resins precharged with potassium (15a, i, j); the ammonium form of these exchangers cannot be given to patients with cirrhosis, since they can precipitate coma (16a). This last point is discussed in greater detail in chapter 14 which deals with cirrhosis and ascites.

### *C. The Use of Diuretics in Increasing Urinary Sodium and Chloride*

In the discussion of the external exchanges of electrolytes in health it was pointed out that the urinary tract was the chief pathway for the excretion of sodium. The renal output of this ion can be increased to a variable degree by diuretic agents (16b).

**1. Water.** It has already been indicated that in normally hydrated subjects with intact salt stores the ingestion of water without electrolytes results in a diuresis of water with but little loss of sodium and of chloride. However, in subjects who have electrolyte excesses and are depleted of water, replenishment will restore glomerular filtration and urine flow and permit the excretion of the extra salt. Similarly, patients with hyposthenuria will require large water exchanges to attain an adequate solute output. These are in all probability the types of patient described in large numbers

by Schemm who has found that the liberal administration of water without electrolytes, up to five liters per day by mouth or by vein, induces diureses (17a-c). However, the routine use of this regimen in all patients with sodium and chloride present in excess is largely unsuccessful in the experience of other clinical groups. Some do respond while the majority of the remainder are unaffected. Many develop circulating or respiratory distress and even actual convulsions, suggesting water intoxication.

**2. Urea.** Urea is frequently overlooked as a simple, cheap, and safe diuretic in patients in whom the blood nonprotein nitrogen is within normal limits or only slightly elevated. It increases urine flow by diminishing the reabsorption of filtrate and can thereby induce the desired salt losses. It can be given as a 40 per cent solution in water or in carbonated beverages for a total daily intake of 40 to 50 grams (18a, b). However if the impetus for the reabsorption of filtered sodium and chloride is high, then only a water diuresis results. This is the case for example in animals depleted of sodium chloride and then given urea (18c). Maximal effects are obtained when urea raises the blood nonprotein nitrogen to 80 or 90 milligrams per cent. If these levels are present as a manifestation of the patient's disease, then additional urea will not increase the urinary output.

**3. Sugars and colloids.** The polyuria and polydipsia induced by hyperglycemia in diabetic subjects, as well as studies in animals, indicate that this and other sugars can be employed to produce an osmotic diuresis. Dextran, which is a polymerized glucose, and other synthetic colloids of this type also function as osmotic diuretics. In experimental studies the increase in urinary excretion is limited largely or entirely to water. In clinical situations however it may touch off an excretion of sodium as well (19a, b). The mode of action under these circumstances is not clear, though obviously in patients with decreased renal blood flow and glomerular filtration these substances will serve to restore circulatory efficiency.

**4. Potassium and acidifying salts.** Bunge was among the first to write of the increase in sodium output which could be induced by potassium administration (20). After the work of Gamble, Blackfan, and Hamilton (20) on inorganic chemicals such as  $\text{NH}_4\text{Cl}$ ,  $\text{CaCl}_2$ ,  $\text{NH}_4\text{NO}_3$  and  $\text{KCl}$  as diuretics, the potassium salts were generally classified as acidifying diuretics, i.e., salts which upon ingestion resulted in a rise in extracellular chloride concentrations and a drop in bicarbonate. In this view,  $\text{NH}_4\text{Cl}$  is absorbed and the ammonium ion metabolized leaving a relative excess of chloride which then displaces bicarbonate. More of the chloride than of the calcium is absorbed when  $\text{CaCl}_2$  is given and again acidosis results. The administration of  $\text{NH}_4\text{NO}_3$  produces a similar hyperchloremia. More recent studies suggest that this results from an accumulation of endogenous chloride which wins out over the polyvalent nitrate ion in the reabsorption of solute



(21a, b). In all of these instances the depression of bicarbonate by chloride lowers the ratio  $\text{BHCO}_3/\text{H}_2\text{CO}_3$  and produces an increase in hydrogen ions in accordance with the mechanisms discussed in chapters 10 and 11.

It is possible that the potassium ion is itself involved in an acidifying effect beyond that to be expected from the associated chloride or nitrate. Elsewhere in chapter 7 it has been indicated that cell potassium depletion is accompanied by a movement of sodium and of hydrogen into cells, resulting in an extracellular alkalosis and a cellular acidosis (22). Potassium replenishment then evicts the hydrogen and sodium and by this indirect mechanism potassium provides hydrogen ions to the extracellular fluid and exerts an acidifying effect. Finally, potassium may produce an acidosis by competing successfully against  $\text{H}^+$  ions in the cation exchange process occurring during the reabsorption of  $\text{Na}^+$  in the renal tubule (23) (see chapters 10 and 11).

Recently it has been reported that in keeping with the original findings of Bunge a high oral intake of potassium minimizes the sodium retention which accompanies cortisone and ACTH therapy during an unrestricted diet. For this purpose 200 or more milliequivalents must be given each day (24a-d).

**5. Xanthines.** Caffeine, theobromine, and theophyllin have long been known to be diuretics by virtue of a multiplicity of pharmacologic effects: they increase cardiac output, they may raise glomerular filtration rates when they are low, and they increase the renal excretion of sodium and chloride. The latter is probably a dual effect; i.e., increased filtration of these ions, when below normal, and decreased tubular reabsorption (25a, b). Their diuretic effects are generally not as pronounced as those obtainable with mercurials and hence they are not often used. Recently Weston has reported that in certain forms of congestive failure the xanthines appear to be useful in conjunction with potassium, digitalis, ammonium chloride, and mercurials (26). The usual dosage is several hundred milligrams.

**6. Mercurials.** The organic mercurials are still the most potent of diuretic agents, acting primarily or solely by interfering with the tubular reabsorption of sodium and chloride. Detailed studies suggest that the primary effect is exerted upon the chloride ion, that this effectiveness is lost when hypochloremia and alkalosis develop, and that ammonium chloride therapy restores or enhances the diuretic response (27a-e). Previous studies raise the possibility that the mercurial diuretics also have an extrarenal action that induces an expansion of plasma volume (27f). If the limitations inherent in most methods of measuring plasma volume permit such a conclusion, this is quantitatively a very minor change.

**7. Carbonic anhydrase inhibitors.** The current view of electrolyte

Patient: E.S. , 61 g W , Congestive heart failure (hypertensive)

Therapy :

Digitalis + low Na diet
Sulfanilamide 4 gm /day

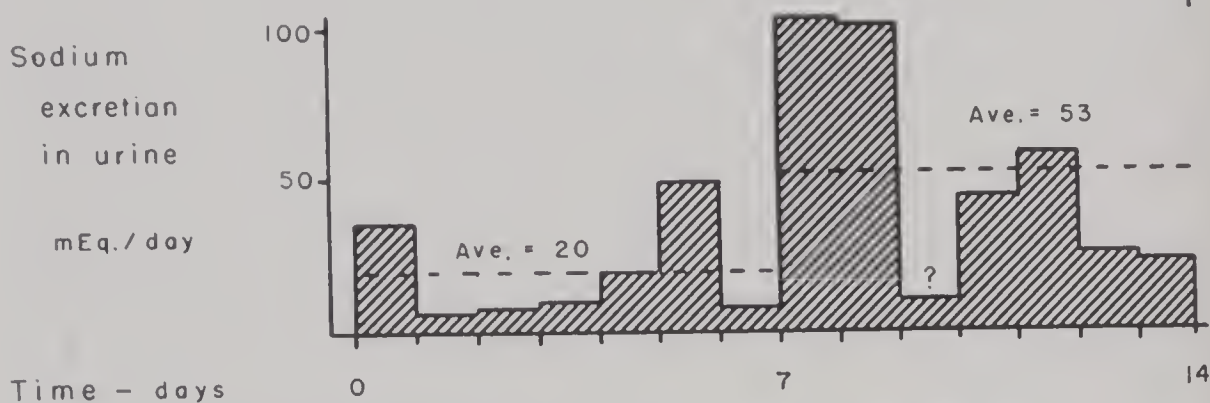


FIG. 9-6. THE EFFECT OF A CARBONIC ANHYDRASE INHIBITOR, SULFANILAMIDE, ON THE RENAL EXCRETION OF SODIUM

The administration of this drug to a patient with congestive heart failure and slowly increasing edema resulted in more than doubling the average daily output of sodium. (From Elkinton (28m).)

transport in renal tubules holds that carbonic anhydrase present in the kidney manufactures carbonic acid from  $\text{CO}_2$  in proportion to the partial pressure of  $\text{CO}_2$ , i.e., the  $P_{\text{CO}_2}$  in body fluids (28a-c).  $\text{H}^+$  ions are thereby provided which then compete with  $\text{K}^+$  to take the place of  $\text{Na}^+$  absorbed from the tubular lumen (see fig. 10-6). Inhibitors of carbonic anhydrase such as sulfanilamide, F6063 or Diamox, and Dirnate interfere with the production of  $\text{H}^+$  ions. This is followed by decreased reabsorption of  $\text{Na}^+$  and increased losses of  $\text{Na}^+$  and of  $\text{K}^+$ . The urine becomes alkaline.  $\text{NH}_4^+$  ion production decreases or ceases, perhaps because of diminished availability of  $\text{H}^+$  ions to unite with  $\text{NH}_3$ . These renal changes can lower the pH of body fluids, raise the chloride level, presumably as an adaptation to the decrease in bicarbonate, and decrease the  $\text{K}^+$ , the  $\text{Na}^+$ , and the inorganic phosphorus in serum as a consequence of increased urinary losses (28d-j).

The increased urinary sodium output following the administration of carbonic anhydrase inhibitors has led to their use in clinical edema (figure 9-6) in a daily dosage of several hundred milligrams (28k-n). Though not always successful, they do open up the exploration of a new class of compounds for this purpose.

### III. Therapy of Potassium Excesses

It has been indicated in the preceding chapter that the only excesses of potassium that appear to be of clinical significance are those present in extracellular fluid, and that in this compartment it is the concentration rather

than the total amount that determines the gravest of the toxic manifestations, i.e., cardiac standstill. There are no data to suggest that increases in either the total amount or the concentrations of cell potassium are deleterious in any gross sense, though certainly the last word on this point has by no means been said. In general terms the elevated concentrations of extracellular potassium can be treated by the following methods, alone or in combination: a) expanding the volume of body fluids, b) removing extracellular potassium by transfer into cells, by excretion via the urine, by gastrointestinal or peritoneal lavage, by exchange resin enemata, or by vivo-dialysis, and c) using known antagonists of potassium, i.e., calcium salts and/or digitalis. The particular method employed will be determined by the etiology of the excesses, the status of the patient, and the means available. This will be illustrated in the discussions which follow. Obviously, irrespective of the method or methods used, all intake or administration of exogenous potassium ions in food, medications, or fluids should be stopped.

#### *A. Correction by Expansion of Body Water*

The administration of solutions which contain no potassium, i.e., glucose or sodium chloride in water, will prove most effective in these patients in whom the hyperkalemia is significantly related to dehydration. This not only lowers the concentrations by dilution but also permits transfers of potassium into cells during the correction of dehydration. In addition the restoration of circulatory efficiency by virtue of adequate fluid replacement and the concomitant use of colloids will permit the renal excretion of this ion to increase. This type of response can be expected to correct the hyperkalemia seen in dehydrated infants who have had diarrhea, in patients with diabetic coma, and, though specific adrenocortical replacement should be added as well, in adrenocortical insufficiency (29a-c). Patients with renal shutdown on the basis of lower nephron nephrosis or potassium intoxication as a result of renal insufficiency, will be helped only to the degree that dehydration is a contributing factor, and to the extent that the body fluids can be expanded with potassium free solutions without precipitating other derangements (30a-d).

#### *B. Correction by Removal of Extracellular Potassium*

**1. Transfer into cells.** It has been pointed out that the cancellation of dehydration will permit the re-entry into cells of potassium previously released to mitigate extracellular fluid deficits. In diabetic acidosis and coma the restoration of carbohydrate metabolism may, by analogy with the blood cell system and brain slices (31a), increase cell potassium. In addition the deposition of liver glycogen and of tissue protein abstracts extracellular potassium. Similar transfers to cells will of course occur in any patient



during the repair phase following food deprivation and losses of cell protoplasm, irrespective of the cause. Again, insofar as these processes may be factors in patients with renal failure and potassium intoxication, we can expect that measure of relief by transfers as a consequence of appropriate remedial procedures.

However, usually glucose and insulin therapy are considered and undertaken in these patients, irrespective of these other factors which have been mentioned, because of the knowledge that these measures in combination can lower the extracellular potassium in normal and abnormal subjects. In this laboratory studies of serum potassium following the administration of only glucose indicate that the potassium frequently does not drop and often may even rise; on the other hand the decrease occurs quite uniformly with insulin administration, alone or with glucose (31b). Hence, both should be used. Unfortunately, this treatment cannot be relied upon to produce or to maintain enough of a decrease to afford more than transient relief, if that.

**2. Urinary excretion.** It is evident from the preceding discussion that this means of alleviating potassium intoxication is open, in the main, only to those patients with dehydration, sodium depletion, or other forms of circulatory inefficiency, but with otherwise intact kidneys. With such pre-renal components corrected, excretion of this ion will rise sufficiently to restore levels to normal. The only forms of renal disease in which one can hope to see this same result are those with a superimposed circulatory defect, and those which fall into the category of resolving lower nephron nephrosis. Mercurial and other diuretics can be expected to be effective only in those patients with kidney tubules that are morphologically and functionally intact.

**3. Gastrointestinal and peritoneal lavage.** Potassium removal by these means can be effective or quite disappointing, depending in great measure upon the mechanics of the individual procedure. Thus, one of us (T. S. D.) has tried gastric lavage for eight hours and removed only a few milliequivalents of potassium despite the fact that vomiting leads to significant potassium deficits. Tubes of the Mahuf type passed into the small intestine are much more effective (32a-d), as are exteriorized loops of small bowel. Colonic irrigations of the ordinary type are apparently not useful for this purpose. This does not apply when they are used in conjunction with cation exchange resins. Peritoneal lavage is, with the exception of the exteriorized bowel loop, the most complicated of these lavage procedures. It can be quite successful if bacterial infection, pH changes, and occlusion of drains by the mesentery are avoided. These techniques are discussed in greater detail in chapter 25.

**4. Exchange resins.** The oral administration of exchange resins not precharged with potassium will augment the fecal output of this ion. This

route of administration is available, however, only in those patients with impending potassium excess, since the depletion is slowly produced and since in patients that develop intoxication intake *per os* is often limited. Elkinton and others have found that carboxylic cation exchange resins in the hydrogen or ammonium form used as high retention enemas (33a-d) are effective in producing prompt lowering of extracellular potassium. One of the cases is illustrated in figure 9-7.

The enema should consist of 25 to 40 grams of resin suspended in 250 to

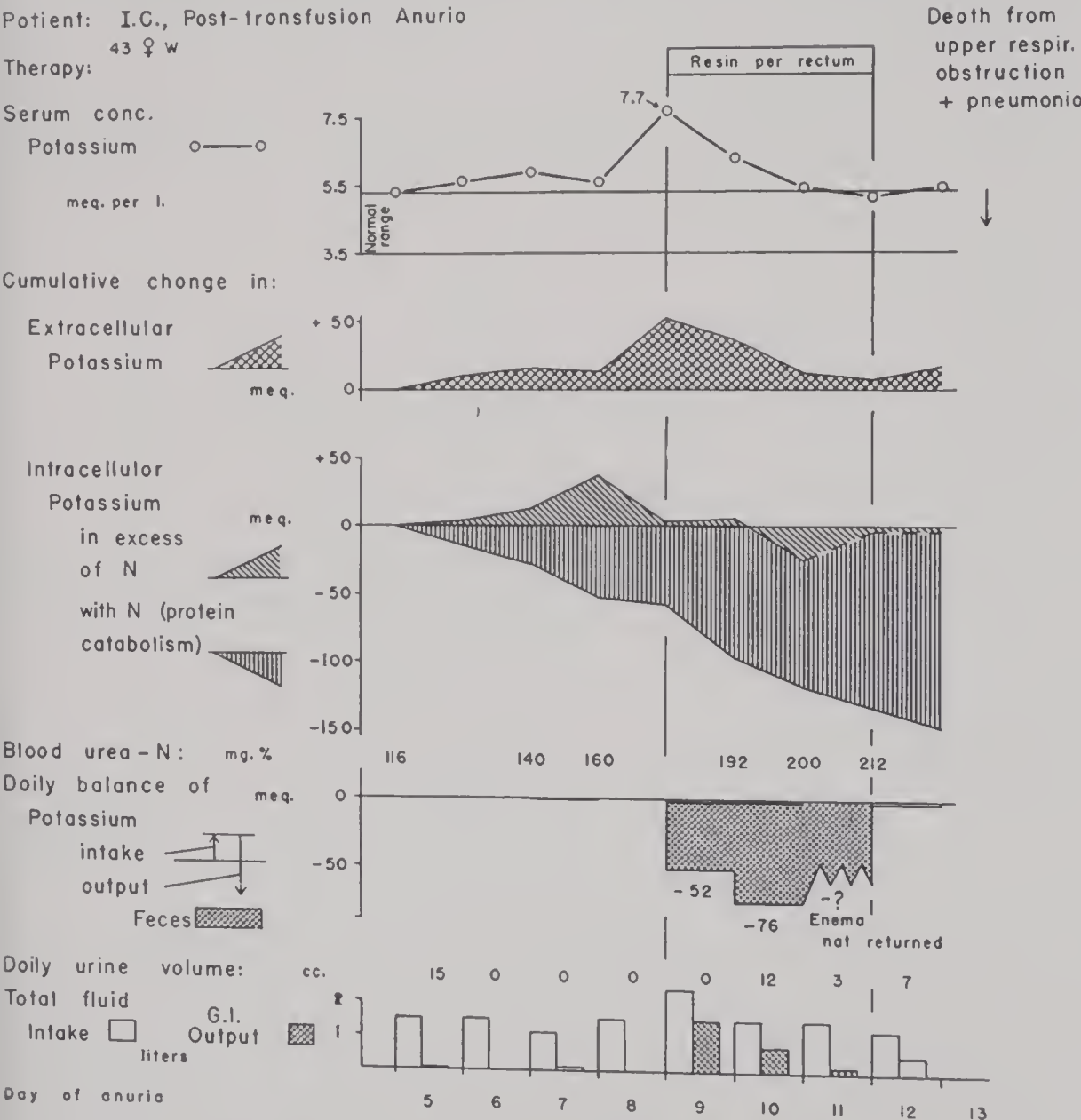


FIG. 9-7. CATION EXCHANGE RESIN PER RECTUM IN THE TREATMENT OF POTASSIUM RETENTION IN ACUTE RENAL FAILURE

A total of 128 mEq. of potassium were removed by means of resin enemas during the first two days of this therapy, with correction of the hyperkalemia. The calculated decrease in total extracellular potassium is compared with the progressive decrement of intracellular potassium during the catabolic process. (From Elkinton *et al.* (33a).)

400 milliliters tap water, injected with a bulb syringe through a large rectal tube as high as possible into the colon. The patient should be encouraged to hold the enema as long as possible; two or three such enemas may be given per day, as indicated by the changing resin level of the ion or the pattern of the electrocardiogram. Up to 76 milliequivalents of potassium per day have been removed in this manner.

When the patient cannot retain the enema, resin may be given by mouth

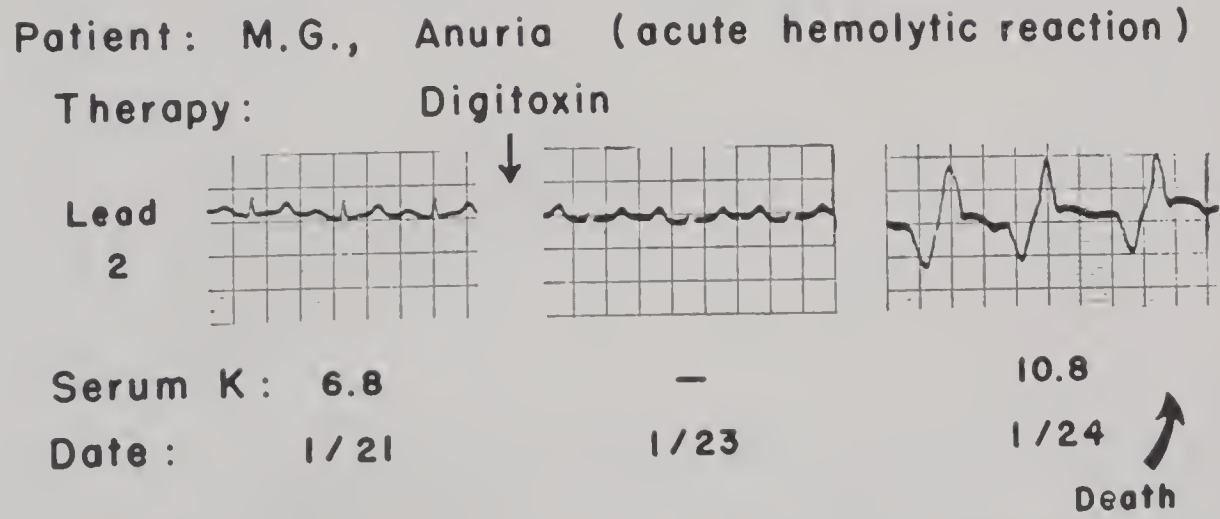
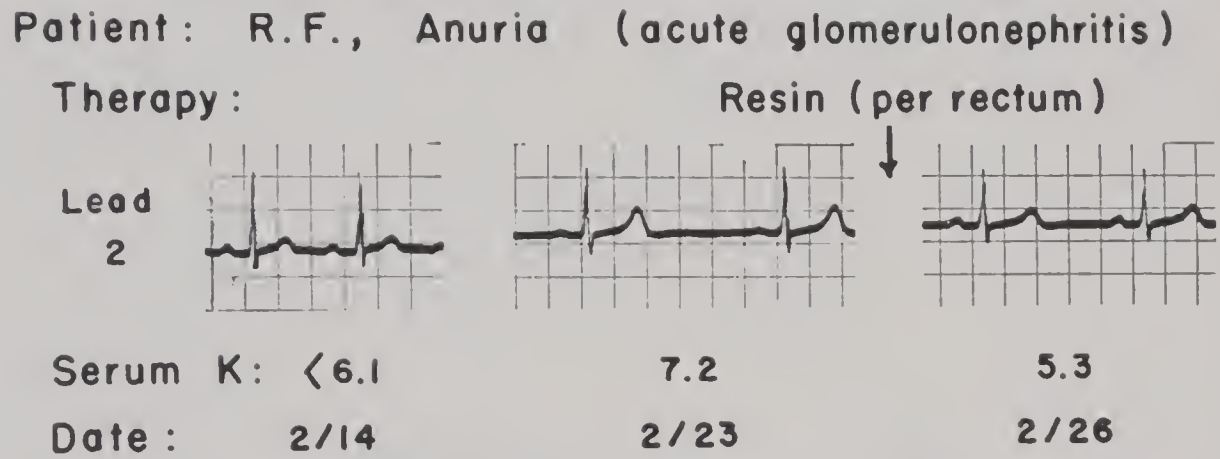


FIG. 9-8. ELECTROCARDIOGRAPHIC TRACINGS ASSOCIATED WITH HYPERKALEMIA IN ACUTE RENAL FAILURE

In Patient R. F. (above), the peaking of the T wave in association with the hyperkalemia is apparent only from examination of serial tracings. The serum K level and the ECG abnormality responded to treatment with resin enemas.

In Patient M. G. (below), there was little ECG evidence of the hyperkalemia on 1/21, and the administration of digitoxin may have obscured a rise in T waves on 1/23 leading to a false sense of security. On 1/24 the ECG showed the extreme effects of hyperkalemia (widening of the QRS complex and fusion with the T wave). This sudden change is a demonstration of the great rapidity with which hyperkalemia may develop. Despite intravenous glucose and insulin the patient died suddenly while preparations were being made for dialysis. Serum K, subsequently determined, revealed a level of 10.8 mEq./l. (From Bluemle and Elkinton (37a).)



or by tube into the stomach when vomiting does not prevent. But resin so given into the upper end of the intestinal tract is not as efficient in picking up potassium ion as when placed in the large bowel. For this reason administration of the resin by enema is preferable in this condition. As might be expected this is not always initially successful and may require repeat attempts. Care must be taken not to use an exchanger precharged with potassium of the type devised for relief of edema.

**5. Vivodialysis.** In institutions where an artificial kidney is available hyperkalemia can be promptly relieved by dialysing the patient. To avoid undesirable depletion or input of ions the dialysing solutions must approximate the ideal extracellular fluid save that potassium is left out or used in lower than average normal concentrations. This difference in concentration

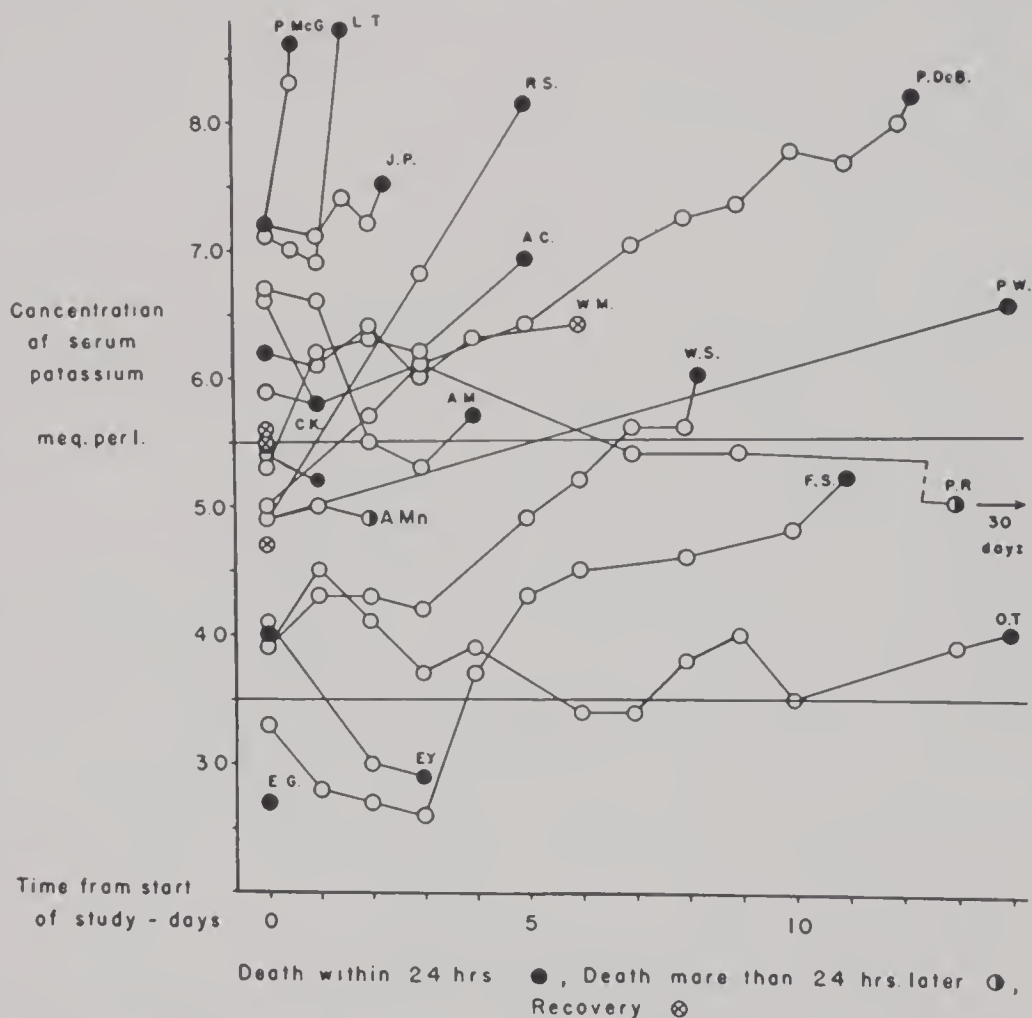


FIG. 9-9. SERUM POTASSIUM LEVELS IN 26 PATIENTS WITH RENAL INSUFFICIENCY AND AZOTEMIA

More values are above than below the normal range and the trend in a majority of the cases is upward. Great variation is evident in the rate of rise of the potassium concentration. The degree of the hyperkalemia correlated well with the degree of oliguria (as shown for the same group of patients in fig. 12-8). (From the data of Elkinton *et al.* (37b, c).)

gradients removes potassium and simultaneously corrects any other deficits or excesses which may be present (34a-e). Incidentally, aside from surgical asepsis within the apparatus and in the actual connections to the patient, the dialysis bath itself need not be sterile since bacteria cannot traverse the intact cellophane membrane. However, there are many other problems inherent in the use of an artificial kidney and hence the entire subject is treated in detail in a separate chapter, number 25, entitled "Vivodialysis."

**6. Known antagonists of potassium.** Animal and clinical studies have identified but two specific antagonists of potassium insofar as its cardiotoxic effects are concerned. These are calcium salts and digitalis (35, 36a, b). They each tend to cancel the cardiac standstill produced by  $K^+$  excesses. Incidentally, this is in keeping with the known synergism of calcium and digitalis, the beneficial effects of potassium in digitalis intoxication, and the appearance of digitalis intoxication in patients who develop potassium deficits while on maintenance amounts of this drug. Sodium chloride has been also used as an antidote, but the mechanism of beneficial action, if elicited, is unknown.

**SUMMARY:** Excesses of water producing hypotonicity can be treated in the anuric by withholding water or by vivodialysis via an artificial kidney with a positive filtration pressure. In hypotonicity of the type which represents resetting of volume and osmoreceptors the only possibly effective approach is one directed at the underlying disease whether it be congestive heart failure, cirrhosis, or nephritis. Sodium administration is of value in hypotonicity only when sodium depletion is present.

Therapy of sodium or potassium excesses involves restriction of intake and augmentation of the removal of these cations via the gastrointestinal tract by irrigation or cation exchange resin administration and via the kidney by means of diuretics. In the case of potassium, excesses in extracellular fluid can also be decreased by transfers into cells or combatted by calcium and digitalis. Finally, vivodialysis is an extremely effective means for correcting disturbances in the concentrations and total amounts of these and other body solutes.

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## *Chapter 10*

# **ANION-CATION BALANCE AND pH: PHYSICO-CHEMICAL AND PHYSIOLOGICAL MECHANISMS**

### **I. Introduction**

The dynamics of anion-cation, or acid-base, balance and hydrogen ion concentration are inseparable from those of the total ionic structure of the body fluids as already propounded in the preceding portions of this book. Nevertheless this aspect of the body fluids warrants separate and careful consideration if the subject is to be adequately understood. Numerous attempts to purvey the fundamental facts concerning anion-cation relationships and hydrogen ion concentrations have convinced the authors that the majority of expositions of the subject assume a background of knowledge which most students and practitioners either do not possess or cannot recall with clarity. The result is discouragement which is compounded by confusion as to the precise definition of many of the chemical and physiologic terms employed. It would appear, therefore, that certain basic chemical concepts need to be reviewed and clarified, and their roles in the more complex biological system then elucidated with precision. For only with clear understanding of the basic principles can the physician adequately diagnose and treat disturbances of this category in his sick patients.

In acquiring such comprehension precise terminology is important. Many students, for instance, are early confused by the use of the terms "acids" and "bases" for "anions" and "cations." In the field of pure chemistry acids usually are defined as substances yielding protons or hydrogen ions with a positive charge; it is disturbing, therefore, to find that negatively charged ions are called "acids." The converse is true of "bases" and "cations." To avoid this confusion we have used as consistently as possible the terms "anions" and "cations" rather than "acids" and "bases," although in the physiological field the latter terms have become time-



honored synonyms for the former. Throughout our presentation of this subject we have attempted to define and to use our terms carefully and as an additional aid to achieving this purpose a glossary of terms is appended to portions of this chapter.

In these two chapters we present what we hope is a reasonably understandable and integrated concept of the physicochemical and physiological processes involved. This includes the role of the hydrogen ion concentration in the body fluids and its physicochemical regulation by a series of buffer systems, and the physiological regulation and readjustment of these buffer systems by organs of exchange with the external environment, namely, the lungs and kidneys. Subsequently we take up the disturbances of this complex system as they occur in disease states, and attempt to indicate the main principles of therapy. For other and more detailed expositions of the whole subject the reader is referred elsewhere (1a-j).

## II. Hydrogen Ion Concentration

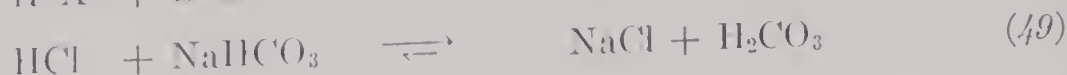
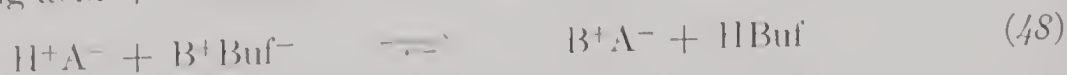
### A. Hydrogen Ions in the Body Fluids

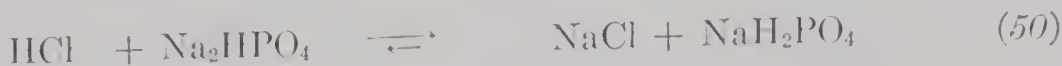
The reaction of the extracellular fluids in the body is slightly alkaline, i.e., the hydroxyl ions,  $\text{OH}^-$ , somewhat exceed the hydrogen ions,  $\text{H}^+$ . Compared to other anions and cations the total quantities of hydrogen and hydroxyl ions are very small, hydrogen ion concentration being of the order of magnitude of  $10^{-7.4}$  gm. ions or Eq. per liter of extracellular fluid or between one ten thousandth and one one-hundred thousandth mEq. per liter. Nevertheless, their relative concentrations, most easily quantitated in terms of pH (see Glossary), are regulated within very narrow limits. It would appear, therefore, that the hydrogen ion concentration of the internal environment closely conditions cellular function and hence its regulation is the object of one of the principal homeostatic systems of the body.

### B. Mechanisms for Maintenance of Hydrogen Ion Concentration

The first defense against undue variation in hydrogen ion concentration is the buffer system. This holds for the body fluids as well as for solutions *in vitro*. A buffer system consists of a weak acid (HBuf) and its salt ( $\text{B}^+\text{Buf}^-$ ) in solution; such salts react with strongly dissociated acids ( $\text{H}^+\text{A}^-$ ) to form a neutral salt ( $\text{B}^+\text{A}^-$ ) and a slightly dissociated weak acid (HBuf). This relationship is illustrated for the principal buffers of the body fluids, bicarbonate, phosphates, and proteins as follows:

Strong acid + buffer salt  $\rightleftharpoons$  neutral salt + weak acid





The effect on hydrogen ion concentration of the addition of a strong acid to the solution, is therefore minimized; the actual decrease in pH being due to the slightly increased dissociation of the weak acid as a result of the common ion effect:



The equation which is the prototype for the effect on hydrogen ion concentration of the buffer systems in the body fluids may be written thus:

$$[\text{H}^+] = k \frac{[\text{HBuf}]}{[\text{Buf}^-]} \quad (53)$$

where  $k$  is the dissociation constant of the acid. In other words, the hydrogen ion concentration of a solution containing a buffer acid and its salt varies directly with the ratio of the acid to the salt. This is a physico-chemical equilibrium.

The buffer systems in the body fluids, which are described in the next section, constitute, therefore, an immediate physicochemical first defense against variability in the hydrogen ion concentration. This defense, however, is limited according to the law of mass action and hence over time would become progressively ineffective were it not for the secondary line of defense, the physiological modification of these buffers by the lungs and kidneys. The homeostatic regulation of hydrogen ion concentration throughout the life of the organism depends on the interplay of these two types of mechanisms.

### C. Glossary

*Electrolyte*: a substance which when dissolved in water produces a conducting medium, i.e., a solution of dissociated atoms or radicles (ions) with positive and negative electrical charges. Example:  $\text{NaCl} \rightleftharpoons \text{Na}^+ + \text{Cl}^-$ ,  $\text{KHCO}_3 \rightleftharpoons \text{K}^+ + \text{HCO}_3^-$ .

*Ion*: a positively or negatively charged dissociated atom or radicle from an electrolyte in solution. Example:  $\text{Na}^+$ ,  $\text{Cl}^-$ ,  $\text{K}^+$ ,  $\text{HCO}_3^-$ .

*Anion*: a negatively charged ion, an atom or radicle with one or more extra electrons. Example:  $\text{Cl}^-$ ,  $\text{HCO}_3^-$ ,  $\text{HPO}_4^{--}$ , categorically symbolized as  $\text{A}^-$ .

*Cation*: a positively charged ion, an atom, or radicle with one or more protons in excess of electrons. Example:  $\text{H}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{++}$  categorically symbolized as  $\text{B}^+$ .

*Hydrogen ion*: a hydrogen atom nucleus, or proton, without its electron, and therefore positively charged. The hydrogen ion of a water solution is hydrated with one atom of water, is called a *hydronium ion*, and is symbolized as

$\text{H}^+ \cdot \text{H}_2\text{O}$  or  $\text{H}_3\text{O}^+$ . For purposes of simplicity, however, hydrogen ion in the body fluids is symbolized as  $\text{H}^+$ .

*pH*: the negative logarithm to the base 10 of the hydrogen ion concentration:

$$\text{pH} \cong -\log [\text{H}^+] \cong \log \frac{1}{[\text{H}^+]}$$

As measured electrometrically, pH is really a close approximation of the logarithm of the reciprocal of  $\text{H}^+$  *activity*, not  $\text{H}^+$  *concentration*.

The "hydrogen potenz" refers to the relative proportions of  $\text{H}^+$  and  $\text{OH}^-$  ions on a scale of 1 to 14. At pH 7 equal amounts are present; above that  $\text{OH}^-$  predominates, below  $\text{H}^+$  is in excess. This scale of arbitrary units permits ease of treating the extremely small quantities involved. The normal physiological range of  $\text{H}^+$  concentration is  $10^{-7.35}$  to  $10^{-7.45}$  Eq. per liter; or 7.35 to 7.45 pH units.

*Acid*: in physiologic use, an anion; in the strictly chemical use, a substance which in solution yields a predominance of hydrogen ions or protons, i.e., a proton donor:  $\text{HA} + \text{H}_2\text{O} \rightleftharpoons \text{A}^- + \text{H}^+ \cdot \text{H}_2\text{O}$ .

*Base*: in physiologic use, a cation; in chemical use a substance which in solution yields a predominance of hydroxyl ions or is a proton acceptor:



*Weak acid*: a proton donor with a low dissociation or ionization constant.

Example:  $\text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-$ .

*Buffer system*: the salt of a weak or poorly ionized acid and the weak acid itself.

When a stronger acid is introduced into such a solution it reacts with the salt to form the weak acid, thereby minimizing or "buffering" the increase of  $\text{H}^+$  ions which would otherwise occur. Example: see equations 48-51. Buffer systems can also be formed from weak alkali, Buf OH, and salt, Buf<sup>+</sup> Cl<sup>-</sup>.

### III. Buffer Systems: Physicochemical Regulation of pH

The principal buffer systems in the various phases of the body fluids are presented in figure 10-1. These consist primarily of bicarbonates, proteins, and phosphates, although many other substances dissociating into weak acids are involved to a minor degree. The physicochemical characteristics of the buffers of whole blood (red cells plus plasma) are best understood since this portion of the body fluids is the most readily available for analysis. From this system, however, indirect information can be derived concerning buffer equilibrium in the interstitial fluids and in the fluids of tissue cells, since the buffers of each phase are constantly reacting with those of adjacent phases, as shown in the figure. The hydrogen ion concentration and the associated anion-cation balance of the body can no longer be considered in terms of the equilibrium of blood alone.



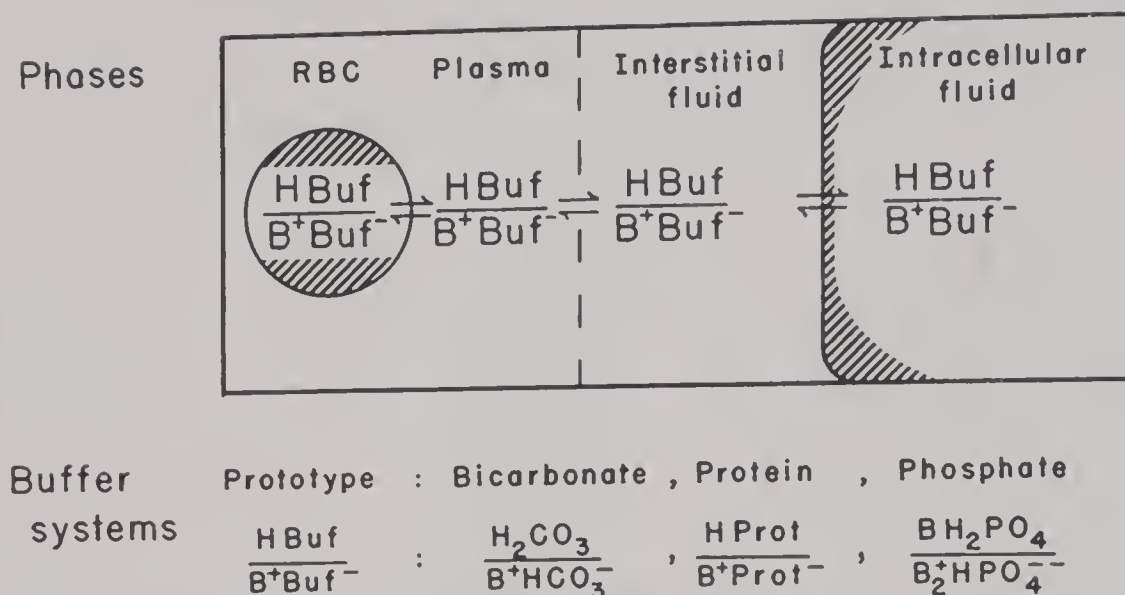


FIG. 10-1. THE PRINCIPAL BUFFER SYSTEMS IN THE VARIOUS PHASES OF THE BODY FLUIDS

The bicarbonate system is quantitatively the largest in the extracellular fluid (plasma and interstitial phases). Protein systems predominate in red cells (as hemoglobin) and in tissue cells as well as in plasma. The phosphate system is small in extracellular fluid; in red cells as organic phosphate and in tissue cells it is of greater quantitative significance.

#### A. The Carbonic Acid-Bicarbonate Buffer System

This is the major buffer system in extracellular fluid and red cells and probably functions to a lesser extent in tissue cells as well. It is peculiarly adaptable to the regulation of hydrogen ion concentration in the living organism because of the constant availability of carbon dioxide from cellular metabolism and because of its easily adjustable excretion through the respiratory tract.<sup>1</sup> The hydrogen ion concentration of this buffer system, as formulated in equation 53, was expressed classically by Henderson (2b) as follows:

$$[\text{H}]^+ = k \frac{[\text{H}_2\text{CO}_3]}{[\text{B}^+\text{HCO}_3^-]} \quad (54)$$

in which  $k$  is the apparent dissociation constant of carbonic acid and  $\text{B}^+$  is the cation dissociated from the bicarbonate salt. This equation of Henderson's was converted by Hasselbalch (2c) to its more commonly used

<sup>1</sup> L. J. Henderson (2a) has suggested that one of the prime characteristics of environment on this planet which facilitated development of living processes was the presence of large amounts of carbon dioxide.  $\text{CO}_2$  is a gas at physiological temperatures, it diffuses rapidly in liquids, and is hydrated to carbonic acid in the presence of water,  $\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3$ . It thus provides an ideal substance for a strong buffer system against wide variations in hydrogen ion concentration. (See chapter 2.)

logarithmic form:

$$\text{pH} \cong \text{pK}' + \log \frac{[\text{B}^+\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]} \quad (55)$$

where  $\text{pK}'$ , as the logarithm of the apparent dissociation constant of carbonic acid activity, has a value of 6.1.

This buffer system, as formulated in equation 54, is really a steady state of disequilibrium maintained in the presence of a large constant cellular metabolic production, transport, and respiratory excretion of carbon dioxide, whose daily turnover is several hundred times as great as the other "structural" electrolytes of the body fluids (see table 23-I). The concentrations of carbonic acid,  $\text{H}_2\text{CO}_3$ , and of bicarbonate,  $\text{BHCO}_3$ , in a ratio of approximately 1:20 are determined respectively by pulmonary excretion and by the renal regulation of the relative concentrations of "fixed" cations and "fixed" anions in the extracellular fluid. Thus organs of exchange with the external environment are physiological regulators of this major physico-chemical buffer system (figure 10-2).

The concentration of carbonic acid in plasma is a function of the partial pressure of the gas,  $\text{P}_{\text{CO}_2}$ , in the pulmonary alveoli; variations in alveolar  $\text{P}_{\text{CO}_2}$ , due to increased or decreased degrees of ventilation, result in corresponding changes in the concentration of carbonic acid,  $\text{H}_2\text{CO}_3$ , in plasma and in the other phases of the body fluids. Such primary alterations in  $\text{P}_{\text{CO}_2}$  lead to the so-called "respiratory" disturbances of anion-

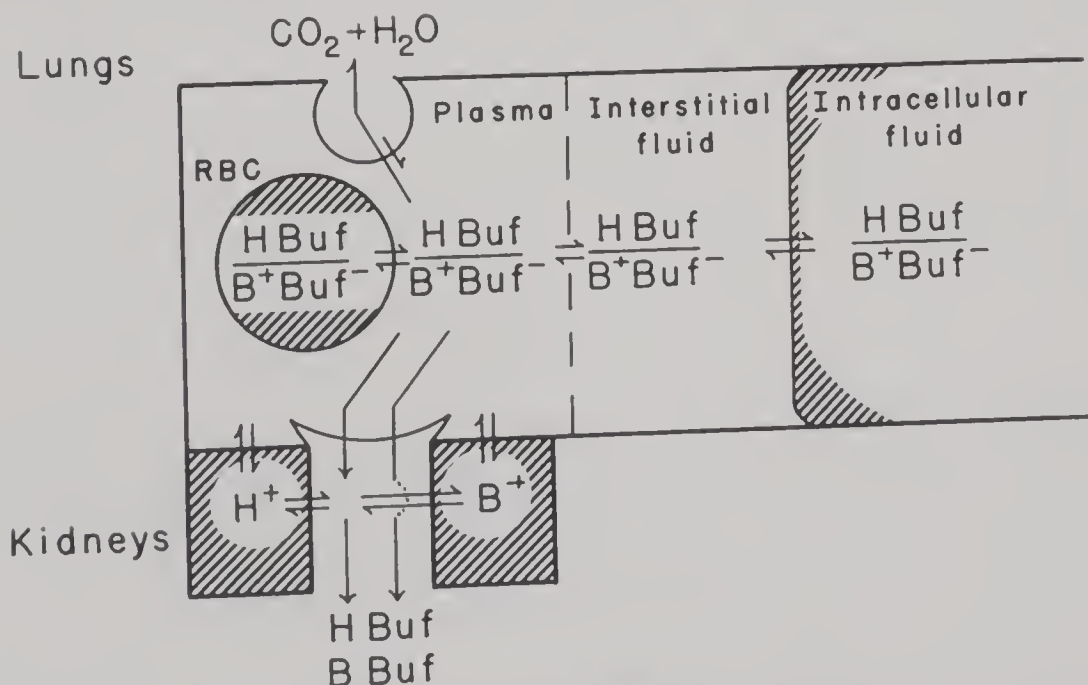


FIG. 10-2. SCHEMATIC REPRESENTATION OF THE PHYSIOLOGIC ACTION OF THE LUNGS AND KIDNEYS ON THE PHYSICOCHEMICAL BUFFER SYSTEMS OF THE BODY SHOWN IN FIG. 10-1.

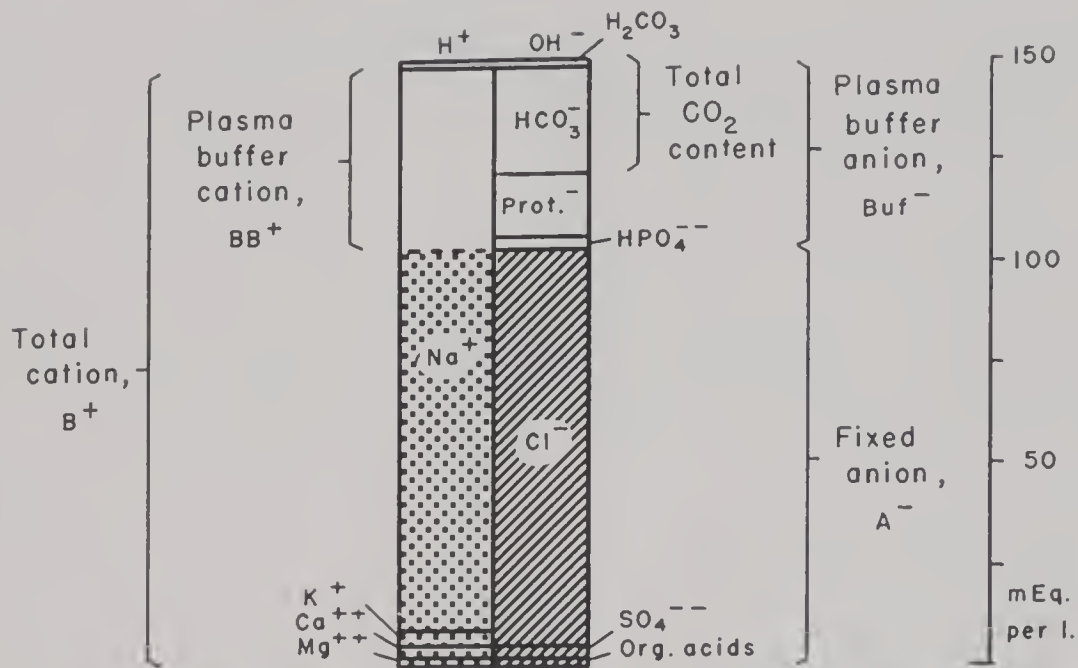


FIG. 10-3. CONSTITUENTS IN ANION-CATION AND pH PATTERN OF PLASMA

The diagram is constructed after the manner of Gamble with the left-hand column showing cations or "bases" and the right-hand showing anions or "acids." Since carbonic acid,  $\text{H}_2\text{CO}_3$ , essentially is un-ionized or undissociated, it is shown undivided at the top and its concentration should be expressed in mM., and not mEq., per liter. The concentrations of free  $\text{H}^+$  and  $\text{OH}^-$  ions are so small that they cannot be shown graphically; of the two ions the latter predominates at the slightly alkaline pH of 7.35-7.45. Buffer anion,  $\text{Buf}^-$ , and its equivalent buffer cation,  $\text{BB}^+$ , is proportionately smaller in plasma than in whole blood because of the greater concentration of protein (hemoglobin) in the red cell.

cation balance. The extracellular concentration of bicarbonate,  $\text{HCO}_3^-$ , on the other hand, is determined by the excess of the sum of fixed cations, ( $\text{Na}^+ + \text{K}^+ + \text{Ca}^{++} + \text{Mg}^{++}$ ), over the sum of the fixed anions ( $\text{Cl}^- + \text{SO}_4^{--} + \text{organic acids}$ ) plus the protein and phosphate buffer anions (fig. 10-3). Bicarbonate thus holds what Gamble has so aptly called the "mendicant" position among extracellular electrolytes. Any renal, gastrointestinal, or metabolic process which alters the relative concentrations of these other cations and anions may produce a change in the concentration of bicarbonate. These are primary changes in bicarbonate concentrations that lead to "metabolic" disturbances of the anion-cation balance; their exact effect on the hydrogen ion concentration of blood, however, must be assessed in terms of the non-bicarbonate, as well as the bicarbonate, buffer systems.

### B. Protein and Phosphate Buffer Systems

The other buffer systems of quantitative importance in the body fluids are those of protein. These consist of amphoteric protein in red cells (hemo-



globin), in plasma (albumin and globulin), and in tissue cells; except for lymph, essentially no protein is present in interstitial fluid (fig. 10-1). Mono- or dihydrogen phosphate ions are present in the extracellular fluid phases in quantities which are insignificant in relation to bicarbonate and protein; in red cells and tissue cells they must play a somewhat larger role. These buffer systems are in linked equilibria with each other and with the carbonic acid-bicarbonate system, donating and accepting hydrogen ions or protons according to the physicochemical laws expounded above. Secondarily they are modified by the physiological action of the lungs on carbonic acid and of the kidneys on the bicarbonate and phosphate (fig. 10-2).

### *C. Use of the Buffer Systems of Whole Blood to Assess the Total Anion-Cation Balance of the Body*

At any given point in time the anion-cation balance and pH of the body fluids can be assessed by chemical measurement of the components of these buffer systems in certain of the body fluid phases. Although the phases available for sampling are restricted to the red cells and plasma, the findings give valid information for the body as a whole because of the physicochemical inter-reactions between the several phases and their buffer systems.

In the past, the "metabolic" changes in anion-cation balance have usually been assessed solely in terms of the concentration of bicarbonate in plasma. This has approximate validity since the carbonic acid-bicarbonate buffer system is quantitatively the predominant one in extracellular fluid. Moreover, changes in the total  $\text{CO}_2$  content of plasma, which is the common biochemical determination, usually indicate changes in the concentration of the bicarbonate ion. This is due to the fact that the other portion of the total  $\text{CO}_2$ , the carbonic acid, constitutes only 1.3 mM. per liter compared to the 24 to 29 mM. or mEq. per liter of bicarbonate. Changes in total  $\text{CO}_2$  content of more than 2 to 3 mM. per liter beyond the normal range, therefore, must indicate change in the bicarbonate ion concentration. With this datum alone the corresponding change in  $\text{H}_2\text{CO}_3$  concentration, or  $\text{P}_{\text{CO}_2}$ , can only be guessed from the clinical circumstances.

As Singer and Hastings (1g) have pointed out, the use of the concentration of total  $\text{CO}_2$  or bicarbonate ion alone provides an incomplete and often misleading evaluation of the anion-cation balance of blood since plasma protein and red cell hemoglobin vary inversely with bicarbonate under changing levels of pH and carbon dioxide pressure (fig. 10-4). The metabolic component of the anion-cation equilibrium, therefore, is accurately quantitated only in terms of the *bicarbonate plus the protein* of whole blood; the phosphate is quantitatively not significant and is included with the protein. To the cationic equivalent of these buffer anions, Singer

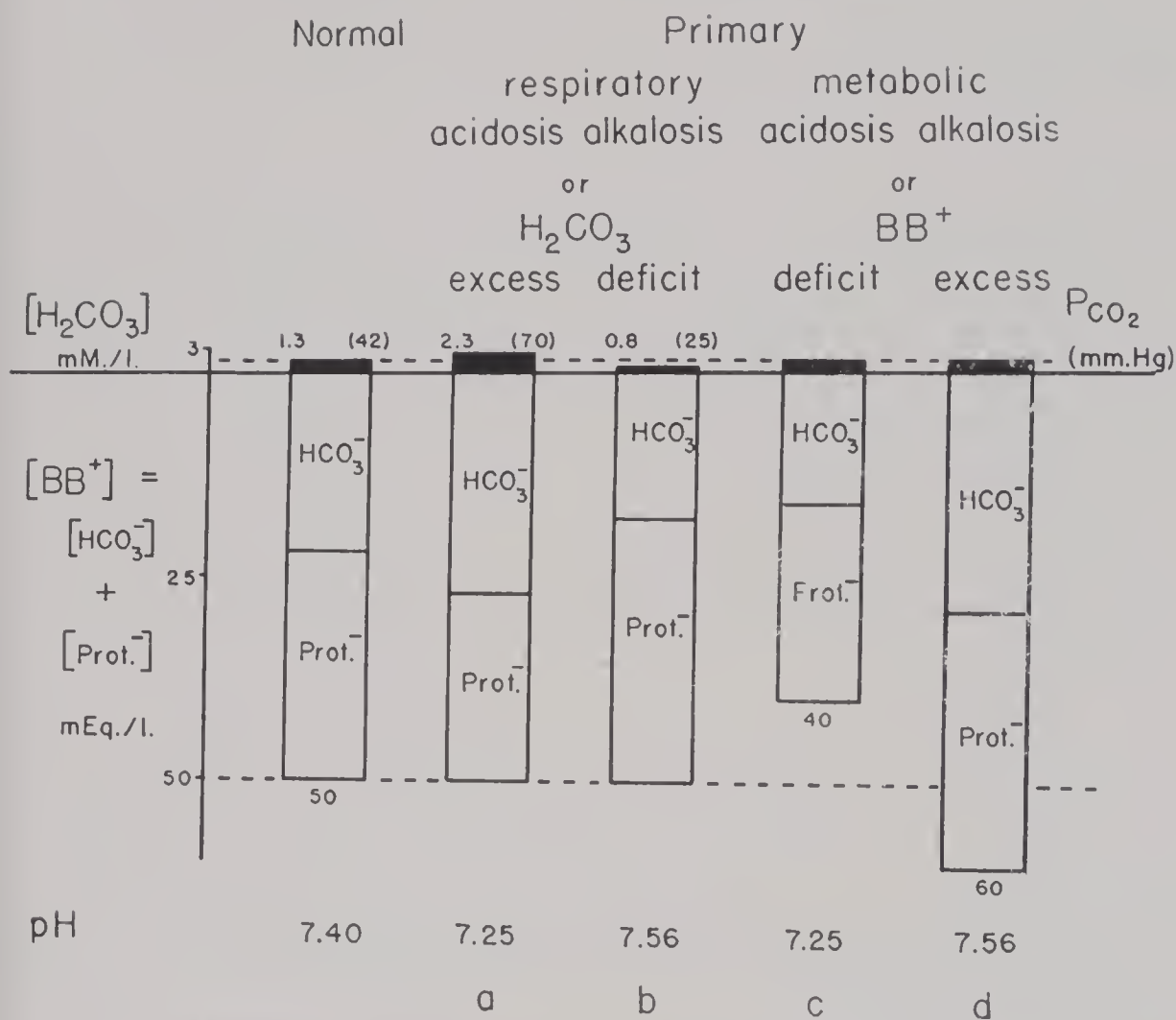


FIG. 10-4. THE FOUR MAIN TYPES OF ANION-CATION DISTURBANCE, AS DETERMINED IN ARTERIAL WHOLE BLOOD

These are presented schematically in terms of the respiratory variable, carbonic acid concentration or pressure of carbonic dioxide, and the metabolic variable, buffer anion or its cationic equivalent. The former is plotted above the line in black and is quantitated in units of mM. per liter of  $H_2CO_3$  above to the left and in units of mm. Hg  $P_{CO_2}$  above to the right. The concentration of buffer anion or its cationic equivalent  $BB^+$ , is plotted downwards in mEq. per liter and is composed of the two anions, bicarbonate and proteinate. The pH values corresponding to each type are shown below the columns. The relative changes in the two buffer anions, bicarbonate and proteinate, composing the total buffer anion or its cationic equivalent are indicated for each pH level. These vary reciprocally in the respiratory disturbances and in the same direction in the metabolic disturbances.

For clear delineation of the primary alterations, secondary or compensatory changes are not shown. (Modified from Gamble (1a).)

and Hastings have given the name *buffer base* (which is designated by the symbol  $BB^+$  in figures 10-3 and 10-4). We prefer to think of  $BB^+$ , however, as "body buffers" or buffer cations, since this eliminates the undesirable term "base." *Buffer cation* is the equivalent of the buffer anion ( $Buf^-$ ):

$$[BB^+] \approx [HCO_3^-] + [Protein^-] + [Phosphate^-] \approx [Buf^-] \quad (56)$$

or can be calculated as the difference between the fixed cations and the fixed acids,

$$[BB^+] = [B^+] - [A^-] \approx [Buf^-] \quad (57)$$

The *calculation* of the two major variables, carbonic acid and buffer base, in the anion-cation equilibrium of the blood is an essential diagnostic procedure in clinical medicine. Actually, five factors characterize the pattern of arterial blood: relative cell volume (hematocrit), pressure of  $CO_2$  ( $P_{CO_2}$ ) or concentration of carbonic acid ( $H_2CO_3$ ), hydrogen ion concentration (pH), plasma or whole blood total  $CO_2$  content (i.e.,  $CO_2$ ,  $H_2CO_3$ , and  $HCO_3^-$ ), and whole blood buffer base concentration ( $BB^+$ ). Given the hematocrit value, the pH of plasma, and the whole blood or plasma  $CO_2$  content  $[CO_2]_b$  or  $p$ , the pressure of carbon dioxide ( $P_{CO_2}$ ) in mm. Hg or the concentration of  $H_2CO_3$  in millimol per liter, and the concentration of whole blood buffer base,  $[BB^+]_b$ , can be readily calculated from the Singer-Hastings nomogram (fig. 10-5). For example if given:

Hematocrit.....	40%
pH.....	7.24
$[CO_2]_b$ .....	15 mM. per l.

Then from the nomogram shown in figure 10-5:

$P_{CO_2}$ .....	38 mm. Hg (normal)
$[BB]_b$ .....	37 mEq. per l. (low)

This defines a primary buffer base deficit or metabolic acidosis since only the buffer base concentration has changed. The range of normal values (1g) for these two factors is:

$P_{CO_2}$ .....	35-45 mm. Hg
$[BB]_b$ .....	46-52

These values are for arterial blood with a normal hematocrit value. It should be noted that the respiratory factor is calculated in this example in units of mm. Hg of pressure of carbon dioxide ( $P_{CO_2}$ ) rather than in milliequivalents per liter of carbonic acid concentration ( $[H_2CO_3]$ ). Since the latter is so small in relation to the concentration of buffer base (fig. 10-3), it is more practical in clinical usage to express the respiratory factor as mm. Hg of  $P_{CO_2}$ .

The measurements from which the calculation of the values for  $P_{CO_2}$  and buffer base are made are the hematocrit, pH, and  $CO_2$  content. These may be made by micro-technics on cutaneous blood (finger prick) arterialized by the prior warming of the hand in a water bath (1g, 3a, b). This method greatly facilitates the accurate assessment of the acid-base balance in many patients. If arterial blood is not readily available, venous samples may be used with the appropriate nomogram.

Thus, from a sample of arterial or arterialized whole blood the state of anion-cation balance and the pH of extracellular fluid can be evaluated. The hydrogen ion concentration is measured directly and is expressed in pH



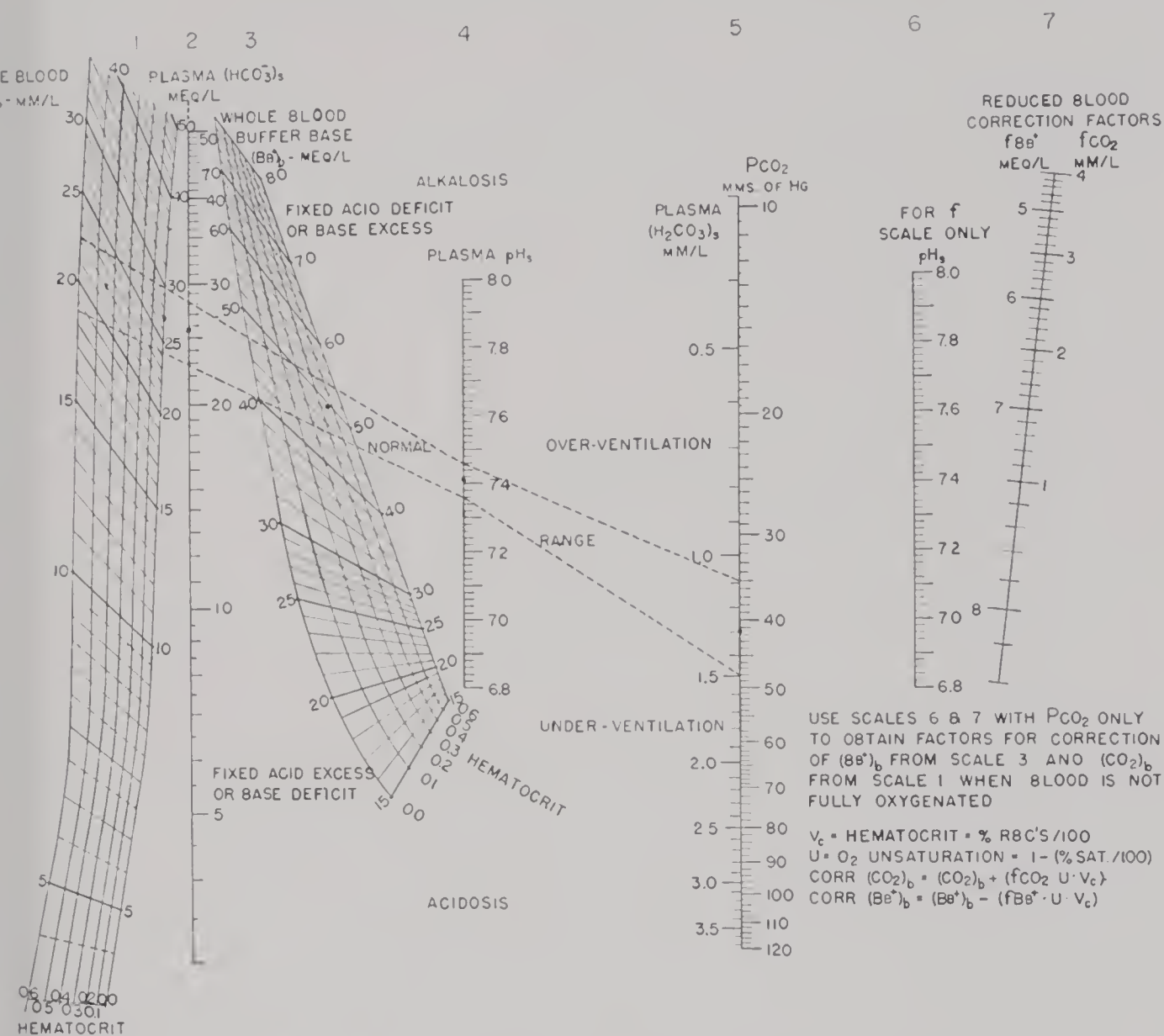


FIG. 10-5. NOMOGRAM OR LINE-CHART FOR THE ACID-BASE BALANCE OF HUMAN BLOOD AT 37°C.

For oxygenated blood (scales 1 to 5) a straight line through points given on two of the scales intersects the remaining scales at simultaneously occurring values of the other variables. The position of this line indicates the kind and magnitude of any disturbance of the acid-base balance. For venous blood or blood with an oxygen saturation of less than 90%, the true values of whole blood  $\text{CO}_2$  and  $\text{BB}^+$  may differ from those obtained by the nomogram rarely by more than  $2\text{mM/L}$  or  $3\text{ mEq/L}$ , respectively. Scales 5, 6 and 7 may be used to correct for this effect of oxygen unsaturation. The "normal range" is for arterial blood. (From Singer and Hastings (1g).)

units. Insofar as *acidosis* is equated with increased hydrogen ion concentration or decreased pH, and *alkalosis* is equated with the opposite changes in hydrogen ion or pH, the diagnosis is made directly. For the understanding and treatment of disease processes, however, it is at least equally important to determine the physiological factors which led to the anion-cation disturbance. These can be assessed for the whole blood sample in terms of the two major primary variables: 1) the concentration of *carbonic acid*,  $[H_2CO_3]$ , or its equivalent, the pressure of carbon dioxide,  $P_{CO_2}$ , and 2) the concentration of buffer anion,  $[Buf^-]$ , (composed of bicarbonate plus protein anion), or its cationic equivalent,  $[BB^+]$ . Since the former component is physiologically regulated by the pressure of carbon dioxide in the pulmonary alveoli, and the latter component is conditioned by metabolic, gastrointestinal, and renal exchanges, quantitation of these two factors provides clues to the type of physiological disturbances of the anion-cation balance which have occurred prior to the time of sampling.

The relationship of these factors and their primary paths of disturbance in disease are shown in figure 10-4. Primary retention or excess of  $H_2CO_3$  leads to a so-called respiratory acidosis (*a*), while primary deficit of  $H_2CO_3$  causes a respiratory alkalosis (*b*). Primary deficit of buffer (due either to reduction in fixed cations or to an increase in fixed anions, or both) results in a metabolic acidosis (*c*); primary excess of buffer (due to a relative increase of fixed cations over fixed anions) leads to a metabolic alkalosis (*d*). These primary disturbances may be *mixed* in that in the same subject the respiratory and the metabolic factors may have undergone primary changes simultaneously and independently. More commonly, however, a primary change in one variable leads to a secondary change in the other. For example, primary retention of  $H_2CO_3$  by the emphysematous lung leads eventually to a secondary renal response consisting of the excretion of the fixed anion, chloride, and an increase in buffer cation. Also primary metabolic deficit of buffer base, as in diabetic acidosis, will be associated with a secondary deficit of  $H_2CO_3$ , achieved by hyperventilation or the Kussmaul type breathing. Such secondary changes effect a more proportionate distribution among the different factors of the buffer systems and are "compensatory" in the sense that they always minimize the change in pH. Occasionally the secondary change so completely counteracts the primary change that the pH is restored to the normal range; in such a case the diagnosis of which is the primary process must be made from clinical, not chemical, data.

These disturbances in anion-cation balance are discussed in more detail in the next chapter. Before turning to that subject it is necessary to consider the mechanisms of physiological regulation of anion-cation balance

by the organs of exchange with the external environment, and to complete the Glossary:

*D. Glossary (continued)*

*Buffer anion*: anions accepting protons or hydrogen ions in the several buffer systems ( $\text{HCO}_3^-$ , protein,  $\text{HPO}_4^{--}$ ); in whole arterial blood the sum of these anions is our index of the metabolic or nonrespiratory primary variable of the anion-cation balance.

*Buffer cation*: the sum of the cations equivalent to the buffer anion.

*Buffer base*: the same as *buffer cation* and equivalent to the *buffer anion*; therefore like the latter is used as an index of the metabolic variable of the anion-cation balance.

*Total  $\text{CO}_2$  content*: all of the  $\text{CO}_2$  which on acidification can be extracted from serum or whole blood without loss or gain of room gases. It consists of the total concentration of the  $\text{CO}_2$  in solution as such, of carbonic acid, of bicarbonate (and in red cells of carbamino- $\text{CO}_2$ ). This total value is often given in volumes per cent and is convertible to millimols per liter by multiplying by the factor 0.45, or dividing by 2.22. The bicarbonate component of the total  $\text{CO}_2$  content, in terms of milliequivalents or millimols per liter, is approximated by multiplying the observed value for the latter in volumes per cent by 0.423. This factor assumes a normal pH and a normal  $\text{P}_{\text{CO}_2}$  value.

*$\text{CO}_2$  combining power*: bicarbonate content of separated serum saturated with  $\text{CO}_2$  at a given pressure (usually 40 mm. Hg), at room temperature and corrected to  $20^\circ\text{C}$ . An "artificial" substitute for measuring total  $\text{CO}_2$  content because respiratory alterations in the  $\text{H}_2\text{CO}_3:\text{B}^+\text{HCO}_3^- + \text{B}^+\text{Prot.}^-$  system are negated, and the value obtained depends on the handling of the blood up to the time of separation of the plasma; is an obsolete method.

*Alkaline reserve*: originally used as synonymous with concentration of bicarbonate; excludes all other blood buffers and is therefore incomplete.

*$\text{P}_{\text{CO}_2}$* : the partial pressure of carbon dioxide; since the gas is in equilibrium with  $\text{H}_2\text{CO}_3$  in aqueous solution, it is equated with the concentration of  $\text{H}_2\text{CO}_3$ .  $\text{P}_{\text{CO}_2}$  is expressed in mm. Hg.

*Respiratory acidosis*: increased hydrogen ion concentration, or decreased pH, due to *carbonic acid excess* resulting from interference with the pulmonary excretion of  $\text{CO}_2$ . Characterized in whole blood by elevation of  $\text{P}_{\text{CO}_2}$  (fig. 10-4, a).

*Respiratory alkalosis*: decreased hydrogen ion concentration, or increased pH, due to *carbonic acid deficit* resulting from augmented excretion of  $\text{CO}_2$  by the lungs. Characterized in whole blood by depression of  $\text{P}_{\text{CO}_2}$  (fig. 10-4, b).

*Metabolic acidosis*: increased hydrogen ion concentration, or decreased pH, due to relative decrease of fixed cation in respect to fixed anion, as a result of "metabolic" and renal processes. Characterized in whole blood by *deficit of buffer anion or buffer base* (fig. 10-4, c).

*Metabolic alkalosis*: decreased hydrogen ion concentration, or increased pH,



due to a relative increase of fixed cation in respect to fixed anion, as a result of "metabolic" and renal processes. Characterized in whole blood by *excess of buffer anion or buffer base* (fig. 10-4, d).

#### IV. Physiological Regulation of pH

The physiological regulation of anion-cation balance and pH consists in modification of the buffer systems of the body fluids by the organs of exchange with the external environment (fig. 10-2).

##### A. Respiratory Exchanges

The principal route of excretion of carbon dioxide is through the lungs. The carbonic acid,  $\text{H}_2\text{CO}_3$ , in the blood equilibrates with the partial pressure of carbon dioxide ( $\text{P}_{\text{CO}_2}$ ) in the pulmonary alveoli. Lowering of the alveolar  $\text{P}_{\text{CO}_2}$  by hyperventilation results in an increased rate of pulmonary excretion of  $\text{H}_2\text{CO}_3$  as  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , and hence in a lowered concentration of  $\text{H}_2\text{CO}_3$  in the blood with a rise in pH. Conversely, elevation of the alveolar  $\text{P}_{\text{CO}_2}$  leads to retention of  $\text{CO}_2$  and an elevated concentration in the blood of  $\text{H}_2\text{CO}_3$ . Since the carbonic acid,  $\text{H}_2\text{CO}_3$ , of blood is in constant equilibrium with the bicarbonate,  $\text{BHCO}_3$ , the  $\text{CO}_2$  in the bicarbonate of blood may be excreted through the lungs, as well as through the kidneys, by any significantly rapid and extensive lowering of the alveolar  $\text{P}_{\text{CO}_2}$ . The partial pressure of carbon dioxide ( $\text{P}_{\text{CO}_2}$ ) in the alveoli is directly dependent on respiratory minute volume. Since the respiratory center is sensitive in varying degree to the three factors of  $\text{P}_{\text{O}_2}$ ,  $\text{P}_{\text{CO}_2}$ , and pH, it is evident that the respiratory regulation of the carbonic acid concentration is an extraordinarily sensitive mechanism for the regulation of one component of the  $\text{H}_2\text{CO}_3:\text{BHCO}_3$  buffer system. Reference to figure 10-5 will emphasize that small changes in the concentration of carbonic acid will mitigate to a great extent the aberrations of hydrogen ion concentration caused by changes of a larger magnitude in the concentration of bicarbonate and buffer base.

##### B. Renal Exchanges

Since most of the cations and anions in the body fluids can be excreted by the kidney, this organ plays a major role in the regulation of anion-cation balance and hydrogen ion concentration. By the differential excretion of fixed anions and cations the kidney conditions the bicarbonate and phosphate buffer systems of the body; in addition the kidney can also excrete directly small amounts of hydrogen ion. The renal mechanisms for the adjustment of anion-cation balance (in contradistinction to the regulation of absolute amounts of solute and water of the body fluids) can best be considered in the two categories of 1) excretion of "extra" anions and 2) excretion of "extra" cations. Both of these processes can be considered in

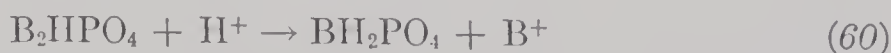
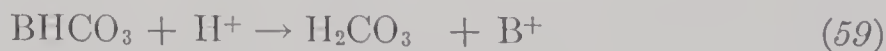
terms of variation in the renal conservation of filtered bicarbonate anion and its accompanying cations.

**1. The excretion of extra anions** is the usual daily task of the kidney since the metabolism of protein and fat steadily produces a certain amount of non-volatile organic acids. Hence, although extracellular fluid is slightly alkaline (pH = 7.35 to 7.45), the urine is usually acid (pH = 5.5 to 6.5). The excretion of extra acids or anions without depletion of the body of the fixed bases or cations ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{++}$ , and  $\text{Ca}^{++}$ ) is accomplished in two ways: 1) by excretion as free acids as the result of an exchange of hydrogen ion for fixed cation, and 2) by excretion with ammonium ion which is produced in the tubular cells of the kidney and which then exchanges for fixed cation. The physiologic evidence at present strongly indicates that the reabsorption of bicarbonate and the production of an acid urine is achieved by a process of ion exchange in the renal tubules (4a-j): hydrogen ion is exchanged to varying degrees across the wall of the tubular cell for cations in the filtrate in the tubular lumen (fig. 10-6). Carbonic acid so formed in the lumen is, in the main, broken down to carbon dioxide and water and reabsorbed to repeat the cycle, while the fixed cation is returned to the blood stream as bicarbonate. In the case of phosphate this results in the conversion of the monohydrogen form,  $\text{B}_2\text{HPO}_4$ , to the dihydrogen form,  $\text{BH}_2\text{PO}_4$ , thereby sparing one cation. Cations neutralizing other weak organic acids may be spared entirely by ion for ion exchange with hydrogen to form free acids. The difference between the concentration of phosphate and the other weak acids at the urine pH and at pH 7.4, is usually termed *titratable acid* and is measured by titration with NaOH.

The secretion of hydrogen ion by the renal tubular cell for the ion exchange process is dependent at least in part on the presence of carbonic anhydrase (c.a.), an enzyme which speeds the hydration of metabolic carbon dioxide to carbonic acid (fig. 10-6):



Experimental inhibition of this enzyme by sulfonamides or derivatives such as F6063, i.e., "Diamox", has provided much of the evidence for the ion exchange mechanism (5a-g). The component parts of this mechanism can be formulated as follows:



The principal cations involved (B) are sodium and potassium.

The salts of strong acids, however, require the ammonia mechanism to





Failure of these renal tubular mechanisms of acidification and ammonium ion formation may result in depletion or "wasting" of the fixed cations: sodium, potassium, and calcium. This explains many of the clinical and biochemical manifestations of renal tubular acidosis, Milkman's osteomalacia, the DeToni-Fanconi syndrome, and certain types of nephrocalcinosis (6a-h), (see chapter 12).

**2. The renal excretion of extra cations** is relatively simple. As bicarbonate ion is always available from metabolic sources, extra cation is excreted as bicarbonate. Since the carbonic acid concentration in urine varies little, as the pH of urine rises larger and larger amounts of filtered bicarbonate escape reabsorption and appear in the bladder urine. The net result is an alkaline urine containing very little ammonia, no titratable acid, and large amounts of bicarbonate.

The tubular reabsorption of filtered bicarbonate appears to be complete

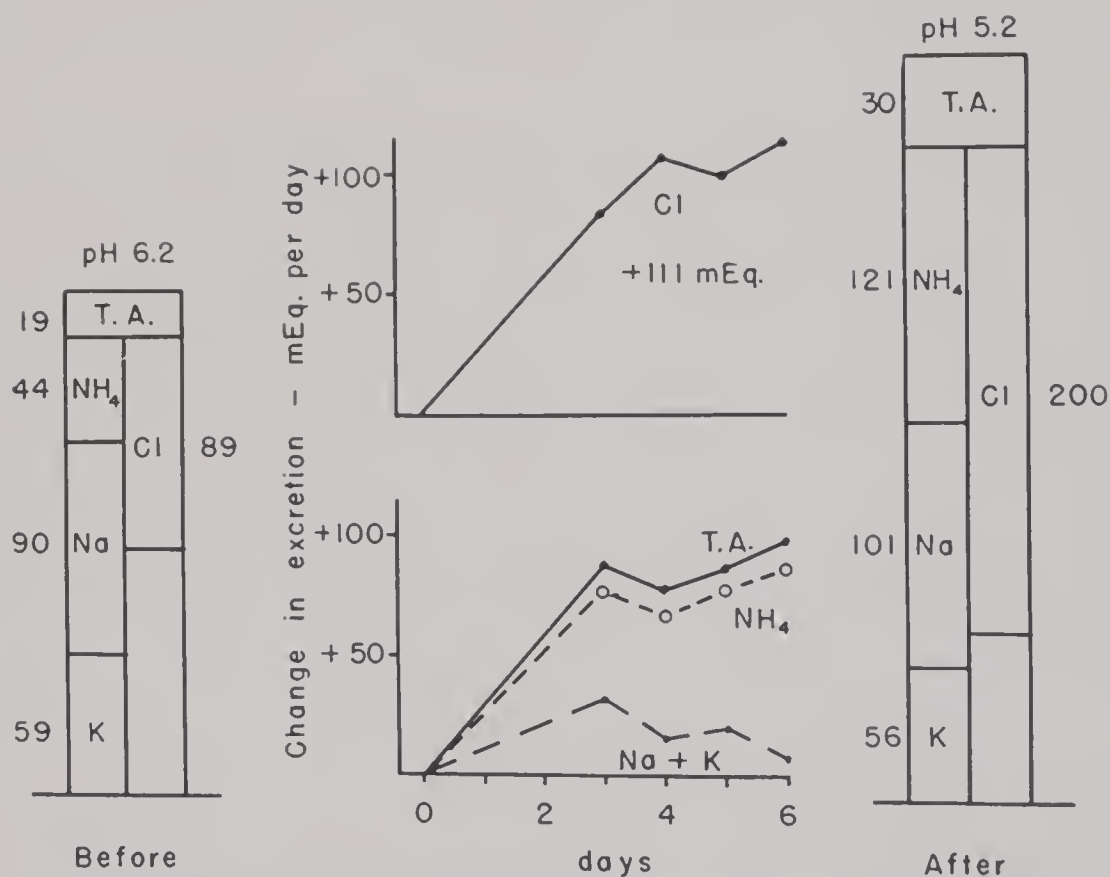


FIG. 10-7. THE RENAL EXCRETION OF AN EXCESS ANION (CHLORIDE)

In the left- and right-hand diagrams, respectively, are shown the pH, titratable acidity, and electrolyte content of a 24-hour specimen of urine before and on the sixth day after the start of the daily ingestion of 112 mEq. of NH<sub>4</sub>Cl. In the center are plotted, above, the change in daily excretion of chloride, and below, the change in daily excretion of fixed base (Na + K) + ammonia + titratable acidity. By the sixth day conservation of fixed base is effected primarily by the production of ammonia and the excretion of an acid urine. (Elkinton *et al.*, unpublished data.)

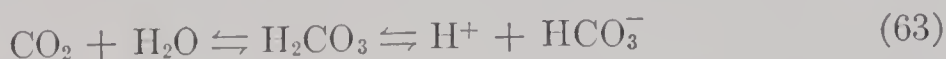
under conditions of metabolic acidosis, while in metabolic alkalosis part of the filtered bicarbonate escapes reabsorption and appears in the urine (4a, b). On the basis of these findings Pitts and associates (4a) formerly postulated that the factor which conditions the tubular reabsorption of bicarbonate is its concentration in extracellular fluid and hence in the glomerular filtrate. More recently, they (4c) and others (4h, i) have presented evidence to indicate that tubular exchange of hydrogen ion, and hence bicarbonate reabsorption, is most directly conditioned by carbon dioxide pressure ( $P_{CO_2}$ ). Experimental evidence by one of the authors and his associates (4j) supports this hypothesis; we found that respiratory alkalosis leads to an increased urinary excretion of bicarbonate although the total  $CO_2$  content (and bicarbonate concentration) decreases in the blood. The converse was true for experimental respiratory acidosis. However, comparison of these data with those obtained during acute metabolic alkalosis strongly suggests that other factors besides  $P_{CO_2}$  are involved in conditioning the tubular reabsorption of bicarbonate; certainly the over-all homeostatic effect is to preserve the hydrogen ion concentration of extracellular fluid.

**3. The renal regulation of anion-cation equilibrium involves exchanges of intracellular as well as of extracellular electrolytes.** That this must be so should be self-evident from consideration of certain experimental and clinical data. These data stem from the original observation of Darrow and his associates (7a) that intracellular potassium deficiency in the skeletal muscle of rats was associated with an extracellular metabolic alkalosis; an observation amply confirmed in other experimental (7b-d) and clinical circumstances (see next chapter, p. 273). Since transfers of cellular potassium of any magnitude, and maintenance of a lowered level of extracellular chloride (and elevated bicarbonate) can only take place through the kidney, such a relationship must involve renal adjustments over time. However, the explanation of the renal mechanisms is not simple. A reciprocal relationship between the tubular secretion of potassium and hydrogen ions (5a) is not an adequate explanation since cellular transfers of hydrogen, sodium, and potassium may take place in directions not predicted by, or in the absence of, such a tubular mechanism (8a, b). Conditioning of the tubular reabsorption of chloride by potassium has also been invoked (8c). Obviously much remains to be done to clarify the renal mechanisms involved and the circumstances under which they operate.

Nevertheless, at present it seems quite clear that intracellular fluid participates in the ionic adjustments to anion-cation disturbances by both an immediate buffering action and by the renal modification of these buffers over more prolonged intervals of time. An attempt to summarize these linked intracellular, extracellular, and renal ionic exchanges is made at the

end of the next chapter following consideration of the clinical disturbances of anion-cation equilibrium.

**SUMMARY:** The initial complexities of acid-base balance and pH can be greatly simplified by thinking in terms of cations (positively charged electrolytes, i.e.,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{++}$ ,  $\text{Mg}^{++}$ ); anions (negatively charged electrolytes, i.e.,  $\text{HCO}_3^-$ ,  $\text{Cl}^-$ ,  $\text{PO}_4^{=}$ ;  $\text{SO}_4^{=}$ ,  $\text{Prot}^-$ , and  $\text{X}^-$  or undetermined acids) and the common ion effect acting through equilibria of the following type:



Thus with retention of  $\text{CO}_2$ , as in asphyxia or in pulmonary fibrosis,  $\text{CO}_2$  accumulates, and the reaction in the above equation shifts to the right. As a consequence more  $\text{H}_2\text{CO}_3$  is formed giving rise to larger amounts of  $\text{H}^+$  and  $\text{HCO}_3^-$  ions. This results in a respiratory acidosis characterized by an increased partial pressure of  $\text{CO}_2$ , i.e.,  $P_{\text{CO}_2}$ , elevated total  $\text{CO}_2$  or bicarbonate content, and a lowered pH. The reverse occurs with hyperventilation which results in undue removal of  $\text{CO}_2$  with a shift of the reaction to the left, as in cerebral lesions, hysteria, and early phases of salicylate poisoning. The actual change in total  $\text{CO}_2$  content may be in this instance quite small.

On the other hand the displacement of  $\text{HCO}_3^-$  by accumulation of ketoacids as in starvation or diabetic coma, or losses of base associated with bicarbonate again permits reaction (63) to move to the right. This obviously results in an increase in the number of  $\text{H}^+$  ions even though bicarbonate is reduced. This represents a metabolic acidosis with a reduced total  $\text{CO}_2$  content and a lowered pH. The converse of this develops when anions such as chloride are lost, as in vomitus, or when sodium associated with bicarbonate increases in amount. In each of these  $\text{HCO}_3^-$  rises and by common ion effect represses the ionization in equation (63) thereby reducing the number of  $\text{H}^+$  ions. A metabolic alkalosis is then said to be present.

In this simplified schema the role of the lungs and the kidney is implicit in these changes in anion-cation balance and in pH but the role of other buffer systems and of the cells has been omitted.

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## *Chapter 11*

### **ANION-CATION BALANCE AND pH: CLINICAL DISTURBANCES AND THEIR TREATMENT**

In the preceding chapter we have presented in some detail the physico-chemical and physiological mechanisms involved in the regulation of anion-cation equilibrium and hydrogen ion concentration in the body fluids. In this chapter we present the disturbances in these equilibria which may occur as the result of disease processes. To clarify further the pathogenesis of these disturbances, each primary type is introduced with a discussion of the production of its experimental prototype. The disturbances are taken up according to the primary alterations of physiological function, respiratory and metabolic; the secondary adjustments are also discussed. At the end an attempt is made to summarize the linked reactions which take place during these disturbances, between the buffer systems in the various phases of the body fluids and the organs of exchange with the external environment.

#### **I. The Dynamic Aspect of Primary and Secondary Reactions**

The sampling of the blood buffer systems at a point in time may lead the unwary to consider the anion-cation disturbances as static phenomena: i.e., certain changes have finished occurring in the main respiratory and metabolic variables. Such a concept is inadequate, for these disturbances are dynamic ones of continuing action and reaction. The primary disturbance, whether respiratory or metabolic, may be waxing, proceeding at a steady rate, or waning, according to the course of the disease and its treatment. The secondary alterations, which constitute the physiologic adjustment or response, take place according to the severity of the primary disturbance, the capacity of the reacting organ to respond, and the factor of time or rate of change involved. For example, the respiratory lowering of carbonic acid concentration which occurs secondarily in the metabolic

acidosis of diabetic coma, will vary according to the degree of metabolic acidosis, the capacity of the lungs to lower the  $P_{CO_2}$ , and the rate of development of the ketosis.

With this concept in mind the reader will not be surprised to discover that primary abnormalities will be found at a given time to be accompanied by a variety of secondary changes. In figure 10-4, in the previous chapter, changes are shown in only one factor in each type of disturbance, and as mentioned in that chapter such primary changes are often accompanied by secondary alterations in the same direction in the other variable. Such secondary changes in the other factor are "compensatory" in the sense that the deviation of the pH is minimized. Where both respiratory and metabolic factors have so changed, an abnormal pH value will usually give the clue as to which is the primary disturbance. Where the pH lies within the normal range, both factors may be disturbed primarily, or the primary variable which has been completely "compensated" for by the secondary variable, can only be identified by other clinical information. Where the respiratory and metabolic factors have varied in opposite directions, both disturbances must be primary. In such instances, of course, their relationship is the opposite of a compensatory one and hence the deviations of pH from normal are severe. Cases illustrating these diagnostic features are presented in this chapter.

## II. Primary Respiratory Disturbances

### A. *Experimental Respiratory Alkalosis and Acidosis*

Primary acute respiratory alkalosis or acidosis can readily be induced in normal subjects by voluntary hyperventilation or by breathing air with a  $CO_2$  content above that normally present in the alveoli. The linked effects on buffer systems and on renal function in these two contrasting disturbances are illustrated in figures 11-1 to 11-3, inclusive. These data taken from studies by one of the authors and his associates (1a-c), confirm, extend, and are essentially in accord with the findings of other investigators (1d-n).

**1. The effect on the blood buffer systems** is shown in figure 11-1. Hyperventilation resulted in a primary drop in  $P_{CO_2}$  or carbonic acid concentration, with no immediate change in concentration of total buffer anion or buffer base; the result was a decrease in hydrogen ion concentration or an increase in pH. Carbon dioxide inhalation resulted in precisely the opposite effect. These results correspond exactly to columns *b* and *a* in figure 10-4, the prototypes of primary respiratory alkalosis and acidosis in arterial blood.

**2. The effect on intracellular buffer systems** was calculated according to the method outlined in chapter 3 (equations 28 to 35). These are illus-

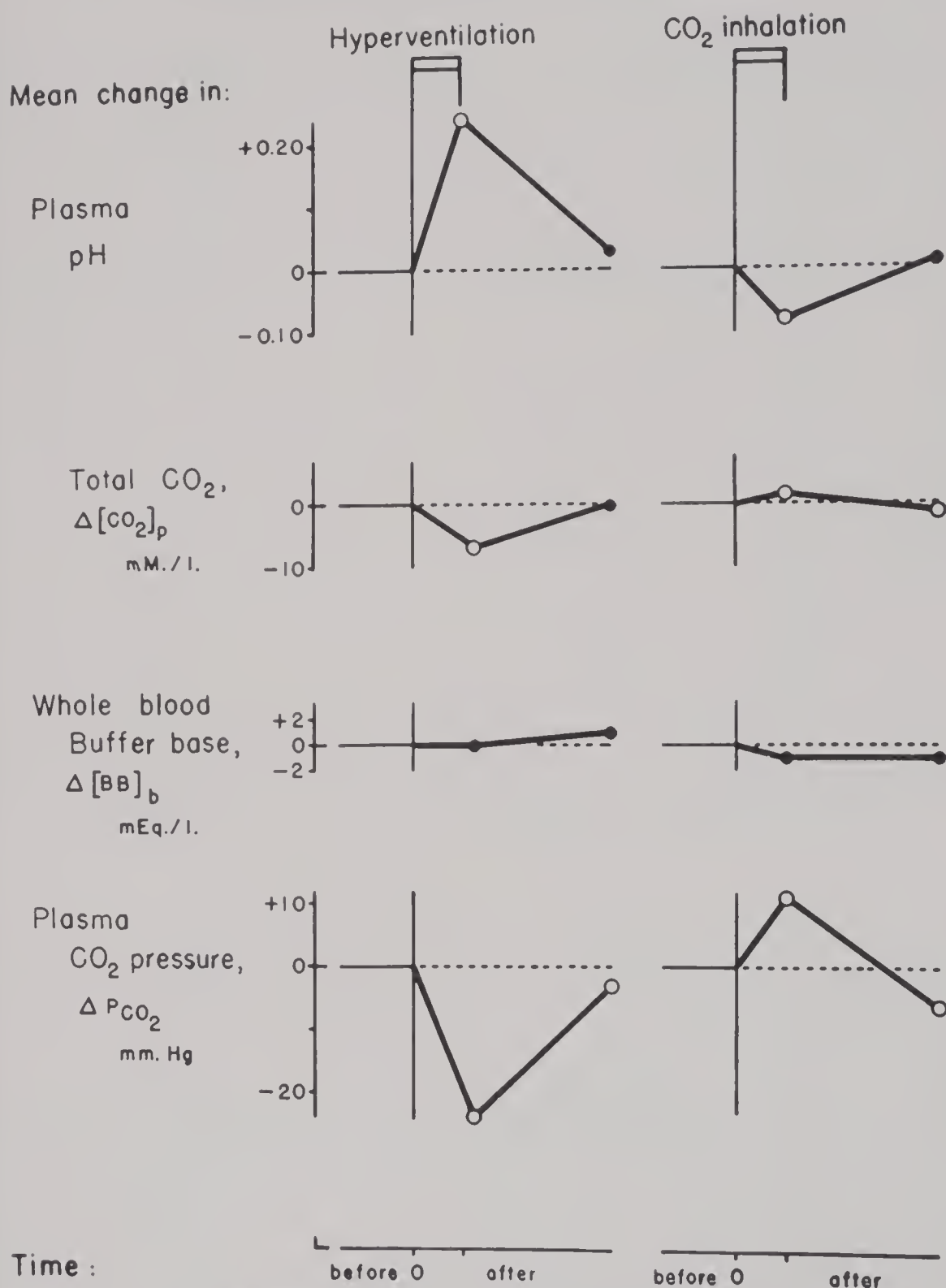
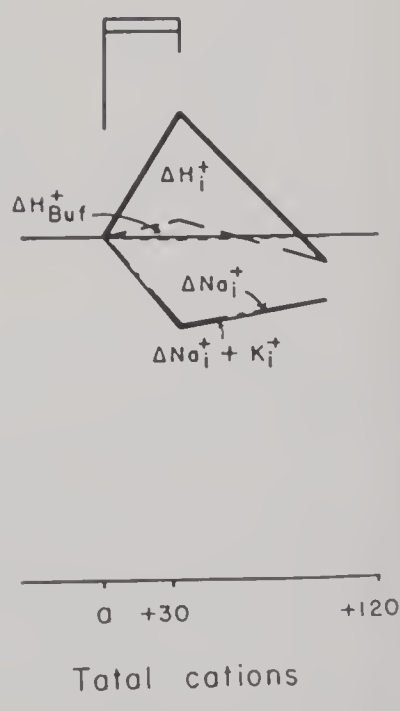
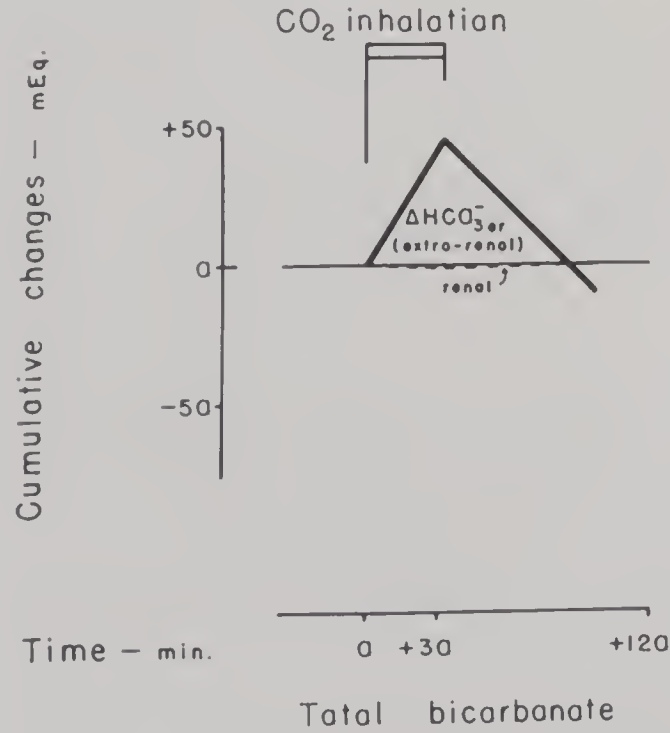
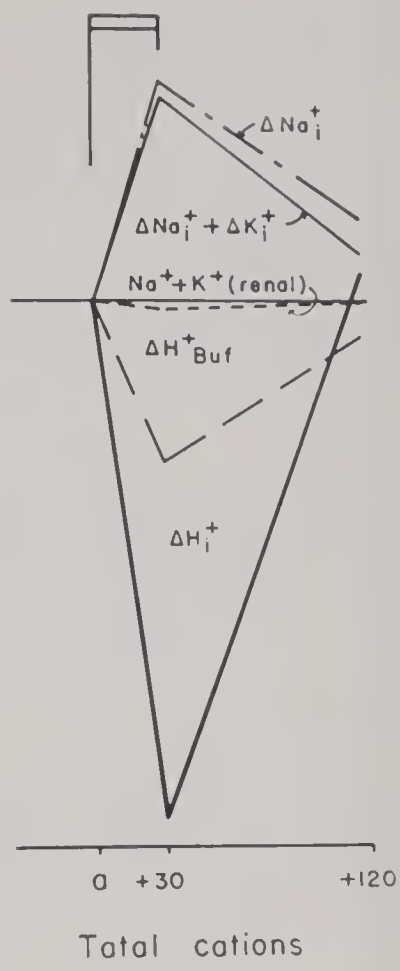
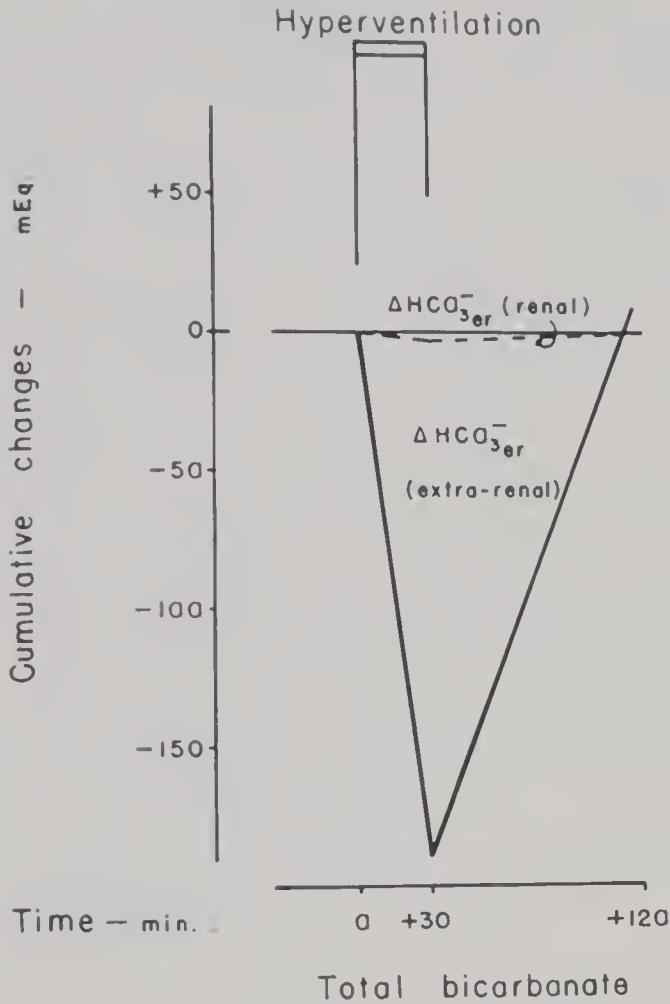


FIG. 11-1. CHANGES IN BLOOD ANION-CATION FACTORS IN ACUTE EXPERIMENTAL RESPIRATORY ALKALOSIS AND ACIDOSIS

The mean changes are shown as observed during and after hyperventilation (respiratory alkalosis) in six subjects and during and after inhalation of 7.5 per cent CO<sub>2</sub> (respiratory acidosis) in six subjects. The changes which are statistically significant for each group ( $p = 0.05$  or less) are designated with open circles.

The CO<sub>2</sub> pressure ( $P_{\text{CO}_2}$ ) fell and rose during the two stimuli respectively, the buffer base concentration was unchanged, and the pH rose and fell accordingly. (From the data of Singer *et al.* (1c).)





trated for the same set of experiments in figure 11-2. It is evident that the major response to both acute respiratory disturbances was an immediate buffering effect by all the buffer systems of the body, including those of the intracellular fluid, and that over the short period of time of the stimulus (30 minutes) renal readjustments were relatively small. These buffer reactions consisted primarily of shifts of hydrogen ion from cellular buffers as well as from those in extracellular fluid and red cells, and at least a partial reciprocal redistribution of sodium between the extracellular and intracellular fluids.

**3. The effect on renal transfers of ions** is shown in figure 11-3. In respiratory alkalosis the rate of excretion of bicarbonate was increased as was that of both sodium and potassium. This suggests inhibition of the hydration of  $\text{CO}_2$  and the secretion of hydrogen ion (fig. 10-6); hence fewer hydrogen ions were available to compete with potassium in exchange for sodium and more of these fixed cations were excreted with bicarbonate in an alkaline urine. In respiratory acidosis the opposite effect obtained and less bicarbonate, sodium, and potassium appeared in a more acid urine.

When these primary disturbances last for periods of hours rather than of minutes, the renal response delineated above has an opportunity to make adjustments of quantitative significance. In prolonged respiratory alkalosis chloride is retained and potassium is lost (2a, b). In respiratory acidosis the opposite appears to occur bicarbonate reabsorption being enhanced with the duration of the acidosis (2c); sodium is transferred out of cells (1j).

### B. Clinical Respiratory Disturbances

Respiratory disturbances in disease are illustrated by the findings in whole blood and serum of certain patients, as shown in figures 11-4 and 11-5.

FIG. 11-2. THE PATTERNS OF RESPONSE OF TOTAL EXTRACELLULAR BICARBONATE AND OF TOTAL BODY CATIONS TO ACUTE EXPERIMENTAL RESPIRATORY ALKALOSIS AND ACIDOSIS

The summated patterns of response are presented for a single experiment of each type. On the left are shown the changes in total extracellular bicarbonate (solid line) and renal bicarbonate (dotted line). On the right the changes in cations are shown: sodium and potassium in urine (dotted line), hydrogen released by blood buffers ( $\Delta \text{H protein}$ ) (dashed line), intracellular hydrogen ( $\Delta \text{H}_i$ ) the difference between the dashed and the solid line, intracellular sodium ( $\Delta \text{Na}_i$ ) (dashed and dotted line), and cellular sodium plus potassium ( $\Delta \text{Na}_i + \Delta \text{K}_i$ ) (solid line).

In both types of experiment the extrarenal response, or tissue cell buffering, greatly exceeds that of the kidney. In acute respiratory alkalosis (upper diagram), the extrarenal loss of bicarbonate is associated in part with release of hydrogen from blood buffer proteins, and in part with hydrogen transferred from cells or bicarbonate transferred into cells. Part of the cellular loss of hydrogen appears to be replaced by the cellular uptake of sodium. Cellular potassium transfers are minimal.

In respiratory acidosis (lower diagram) the transfers are in the opposite direction although to a much lesser degree because of the difference in stimulus. (From the data of Elkinton *et al.* (1c).)

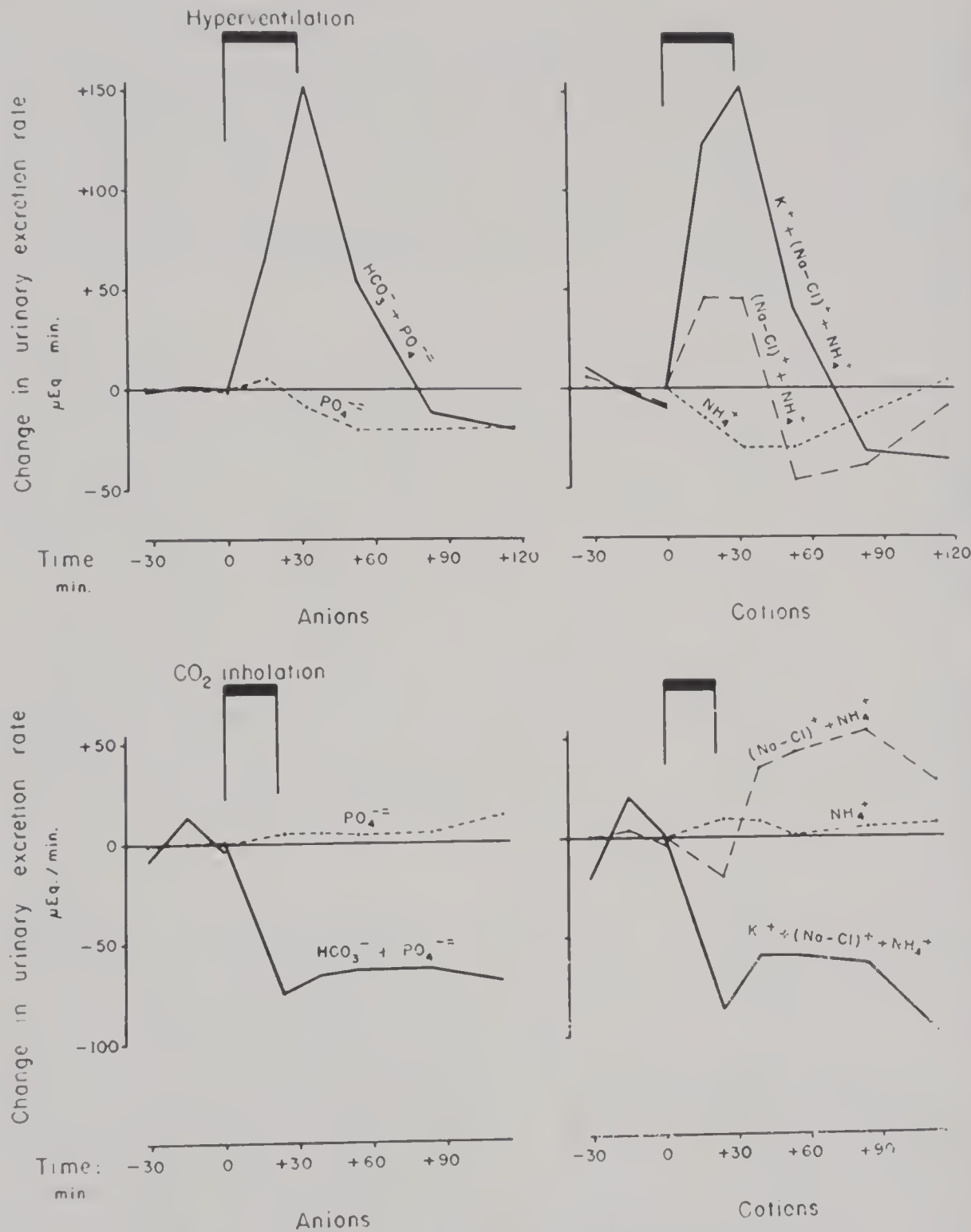


FIG. 11-3. THE URINARY ELECTROLYTE RESPONSE TO ACUTE EXPERIMENTAL RESPIRATORY ALKALOSIS AND ACIDOSIS

The summated patterns of response are presented for a single experiment of each type. On the left are shown the changes in excretion rate of anions from the mean control level; on the right, of cations including the quantity of  $\text{Na}^+$  in excess of  $\text{Cl}^-$ .

In acute respiratory alkalosis (upper diagram) the principal anionic response quantitatively is an increase in excretion of bicarbonate while that of cations is predominantly an increase in potassium. In acute respiratory acidosis (lower diagram), the opposite is true: bicarbonate and potassium are decreased; the changes in excretion rate, however, did not return to the control level. (From the data of Clark *et al.* (1a, b).)



**1. Primary respiratory acidosis or carbonic acid excess** may result from any pulmonary or central condition which interferes with air exchange and excretion of carbon dioxide by the lungs. These include *chronic emphysema, asthma, pulmonary fibrosis, bronchial obstruction, infection, poliomyelitis*, and, in some instances, *congestive heart failure* (fig. 11-4, a,b) (3a-k). It may occur acutely during surgical anesthesia (3l-o). A secondary increase in buffer cation usually is found in chronic cases and is accomplished through the kidney by increased excretion of chloride relative to bicarbonate. The resulting hypochloremia and elevated bicarbonate concentration in serum (fig. 11-5, b) must be clearly distinguished (by clinical data or by pH determination) from a metabolic alkalosis, since the therapeutic indications in the two conditions are completely different.

Therapy of chronic respiratory acidosis is difficult (4a-c). The most important factor is treatment of the underlying pulmonary insufficiency by antibiotics, mechanical clearing of the respiratory passages, digitalization, and, in severe cases, by use of a mechanical respirator or "iron lung" (3p-s,

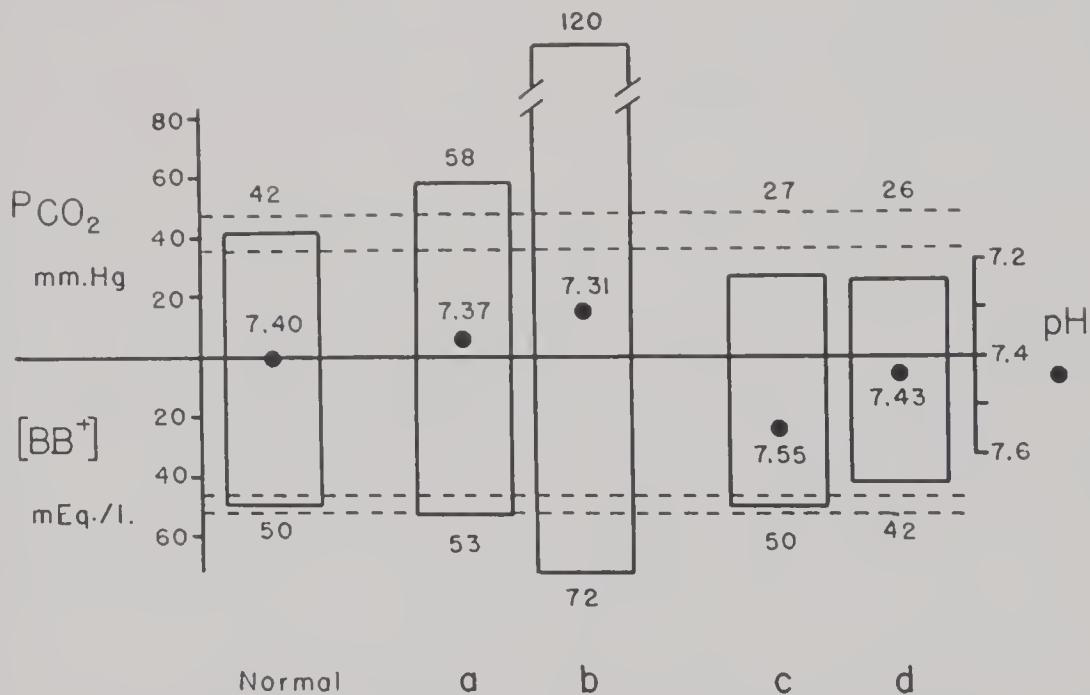


FIG. 11-4. PRIMARY RESPIRATORY DISTURBANCES: ACIDOSIS (a, b) AND ALKALOSIS (c, d)

The respiratory component,  $P_{CO_2}$  or  $H_2CO_3$ , of acid-base equilibrium is plotted upward, and the metabolic component, buffer base ( $BB^+$ ), downward from the midline. The normal range of each is indicated by broken lines, and the normal pattern is shown to the left. Values for pH are represented by the black dots.

The data shown indicate primary respiratory changes in  $P_{CO_2}$  with varying degrees of a secondary response in ( $BB^+$ ), in the following conditions:  $CO_2$  retention in congestive heart failure (a), in chronic pulmonary fibrosis and emphysema (b),  $CO_2$  deficit in constrictive pericarditis with anoxia (c), and in a subject acclimatized to high altitudes (d). (From studies by Singer, Elkinton *et al.*, and from Dill (4d).)

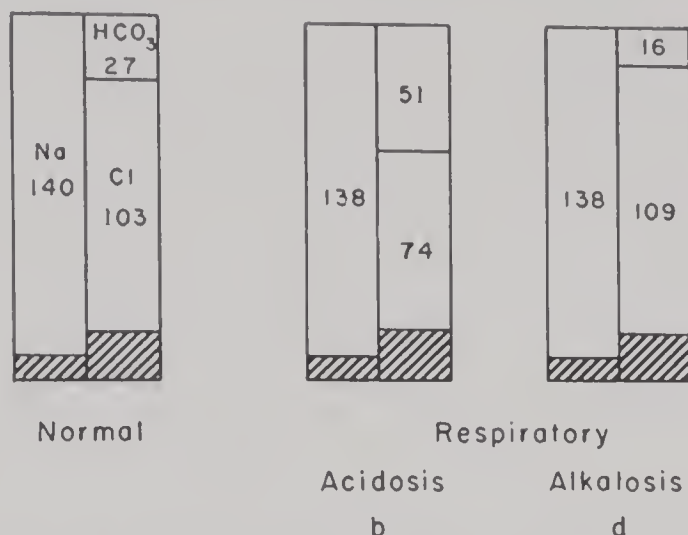


FIG. 11-5. SERUM ELECTROLYTE PATTERNS IN PRIMARY RESPIRATORY DISTURBANCES

The concentrations of the principal serum electrolytes are shown in cases of respiratory acidosis and alkalosis. These data are from the cases with the corresponding letters, *b* and *d* in fig. 11-4. In *b*, a patient with chronic pulmonary insufficiency, the elevated total CO<sub>2</sub> and HCO<sub>3</sub><sup>-</sup>, and lowered Cl<sup>-</sup>, concentration indicate chiefly the compensatory increase in buffer anion and base which is secondary to the carbonic acid excess. The converse is true in the case of chronic respiratory alkalosis resulting from acclimatization to high altitude, shown in *d*.

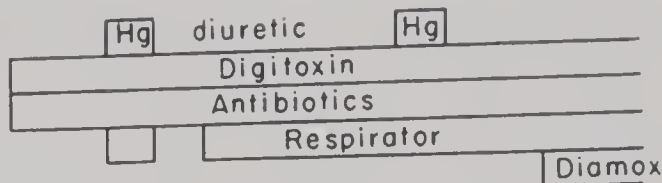
4c). Oxygen must be administered with great care since apnea and coma may be induced. This is due to the loss of sensitivity of the respiratory center to the high levels of CO<sub>2</sub>, and oxygen removes its remaining anoxic stimulus (3t-w, 4b). Recently the carbonic anhydrase inhibitor, "F6063" or "Diamox" has been recommended (3x-z, 4a), but the rationale and efficacy of its use have not yet been established. The temporary results of these methods of therapy are illustrated in figure 11-6.

**2. Primary respiratory alkalosis or carbonic acid deficit** is probably the least commonly diagnosed of the four primary types of disturbance. It is always due to a central respiratory stimulation and hyperventilation which may occur as the result of emotional upset, anoxia, fever, encephalitis, brain tumor, intracranial surgery, salicylate poisoning, or some other less well-defined stimulation (4d-i) (figure 11-4, c, d). Occasionally severe metabolic acidosis may lead to a primary excitation of the respiratory center, as described below under *Mixed Disturbances*. Although the secondary buffer and renal responses in chronic cases have not been adequately defined, evidence suggests that the relative excretion of bicarbonate over chloride, associated with sodium and potassium, leads to a compensatory decrease in buffer anion and base (fig. 11-4, d). Associated patterns of serum electrolyte concentrations are illustrated in figure 11-5, d.

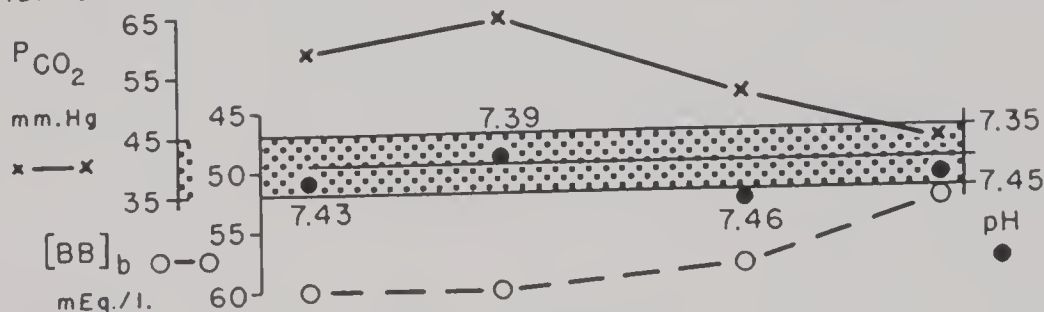
The hyperventilation of respiratory alkalosis may or may not be evident

Patient: I.M., 63 ♂ W

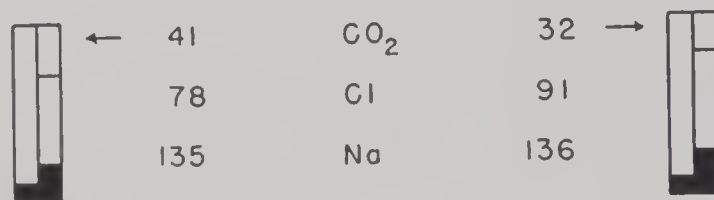
Therapy



Arterial blood:



Venous serum  
conc.:  
mEq./l.



Time - days

FIG. 11-6. ANION-CATION BALANCE AND pH OF BLOOD AND SERUM DURING TREATMENT OF A PATIENT WITH CHRONIC PULMONARY INSUFFICIENCY AND CONGESTIVE HEART FAILURE

Because the pH values lay essentially within the normal range, the diagnosis of a mixed disturbance of 1) primary respiratory excess of  $H_2CO_3$  and 2) primary metabolic excess of buffer cation or base was made clinically: the former on the basis of history, signs, and symptoms of asthma and emphysema, the latter from the signs of peripheral edema and the history of its treatment with mercurial diuretics. The respiratory excess of  $H_2CO_3$  is characterized by the high  $P_{CO_2}$ , the metabolic excess of buffer base by its high concentration. The high total  $CO_2$  content and low chloride concentration of serum are common to both. The items of therapy of this refractory case are indicated at the top of the diagram. (Unpublished study by Winegrad, Jacobus, and Elkinton.)

clinically. If it is, it frequently can be differentiated from the compensatory hyperventilation of metabolic acidosis by the presence of tetany (4e, g, i). Even without overt hyperventilation, the signs and symptoms of tetany are usually present to a varying degree: paresthesias of extremities, frank carpopedal spasm, catatonia, coma, and positive Chvostek and Trousseau signs. The immediate treatment of choice is to increase the content of carbon dioxide in inspired air by rebreathing into a bag or a mask connected to a supply of  $CO_2 + O_2$ . This is followed by attempts at eradication of the underlying cause.



### III. Primary Metabolic Disturbances

#### A. *Experimental Metabolic Alkalosis and Acidosis*

Primary metabolic alkalosis may be produced experimentally by the ingestion or infusion of alkaline solutions such as sodium bicarbonate and sodium lactate which supply fixed cation in excess of fixed anion (1d, 5a-c). Metabolic alkalosis may also be produced by the primary induction of intracellular potassium deficiency (5d, e) (see pp. 256, 273). The effect of these procedures on the buffer systems of the blood is to increase the buffer anion and base with a consequent rise in pH. In addition, ionic exchanges take place between the extracellular buffers and those in the intracellular fluid. The pulmonary response is one of decreased ventilation with a compensatory rise in  $P_{CO_2}$  and the concentration of  $H_2CO_3$ . In the kidney the exchange of hydrogen for sodium and potassium is inhibited with a resultant increase in excretion of the latter cations with bicarbonate.

Primary metabolic acidosis may be produced experimentally by the ingestion or infusion of fixed anion in excess of fixed cation, such as  $NH_4Cl$ , or by metabolic production of organic acids, as in experimental diabetic ketosis (6a-e, 7a-b). The effects on the buffer systems of blood and intracellular fluid, on the pulmonary excretion of  $CO_2$ , and on the kidney, are essentially the converse of those described for metabolic alkalosis in the preceding paragraph.

The over-all responses to both types of these disturbances are delineated in the concluding section of this chapter.

#### B. *Clinical Metabolic Disturbances*

Metabolic disturbances in disease are illustrated by the findings in whole blood and serum of certain patients, as shown in figures 11-7, 11-8, and 11-9.

**1. Primary metabolic acidosis or buffer anion and base deficit** occurs in any clinical situation in which fixed anions increase in relation to fixed cations (i.e., the former may rise, the latter may fall, or both). In *diabetic ketosis* the ketone acids displace bicarbonate, and fixed cations (sodium and potassium) are lost in the urine with the excess anion (7a-c). In the *uremic acidosis* of renal insufficiency, retention of fixed anions (phosphates, sulfates, and organic acids) displaces bicarbonate (fig. 11-7) (7d, e). "*Chloride acidosis*" is frequently seen in patients who have received large amounts of ammonium chloride and other acidifying diuretics or cation exchange resin (6a, b, 7f, g) as well as in those with inadequate renal function who have received large amounts of sodium chloride solution.

The retention or production of any abnormal organic acid, such as salicylate, boric acid, paraldehyde, and methanol poisoning, may lead to metabolic acidosis (8a, 3i, 4h, 7h), although frequently there is a mixed dis-

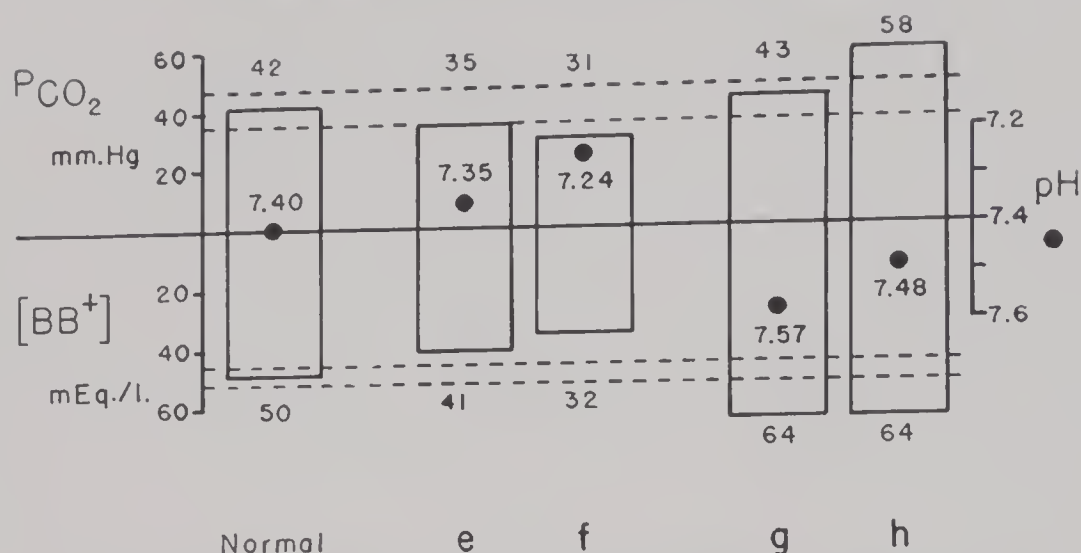


FIG. 11-7. PRIMARY METABOLIC DISTURBANCES: ACIDOSIS (*e*, *f*) AND ALKALOSIS (*g*, *h*)

The data shown in *e* and *f* indicate primary changes in (BB<sup>+</sup>) with varying degrees of a secondary response in P<sub>CO</sub><sub>2</sub> in chloride acidosis due to NH<sub>4</sub>Cl administration and in uremic acidosis as a result of chronic glomerulonephritis. Similar changes are observed, though not illustrated here, in the primary metabolic acidosis produced by losses of sodium or by excesses of endogenous anions, as in diabetic coma, or excesses of foreign anions such as borate or salicylate.

In the last two columns of the figure, *g* and *h*, alkalosis due to gastric suction and alkalosis with potassium deficiency following ACTH therapy are illustrated. Administration of excessive amounts of sodium with bicarbonate or with a metabolizable anion such as acetate will also produce a primary metabolic alkalosis. (Elkinton *et al.* (Sb, 10p).)

turbance (see below). All these types of metabolic acidosis involve failure of the kidney to excrete excess anions and to conserve fixed cations; the result is a deficit of buffer base (fig. 11-7, *e*, *f*). This is always accompanied by a secondary deficit of carbonic acid achieved by hyperventilation (Kussmaul breathing). Such a compensatory response is more likely to be partial than complete in terms of pH preservation. The serum electrolyte pattern found in a patient with uremic acidosis shown in figure 11-8, *f*; with increased concentrations of the fixed anions (phosphate, sulfate, and organic acids) and with the decreased level of total CO<sub>2</sub> and bicarbonate is typical. A lowered sodium concentration also contributes to the diminished bicarbonate and total buffer anion and base. (See also figs. 12-5, 13-5, and 15-8).

The clinical manifestations are frequently, but not always, hyperventilation (Kussmaul breathing), stupor, and coma; in uremies twitching or convulsions may appear. Despite the presence of hyperventilation, tetany is absent. Azotemia, hyperglycemia, ketonemia, glycosuria, and ketonuria, if present, are helpful in the differential diagnosis. Treatment of course depends upon the pathogenesis of the acidosis. If the total buffer anion and base is reduced because the patient is depleted of sodium, then obviously

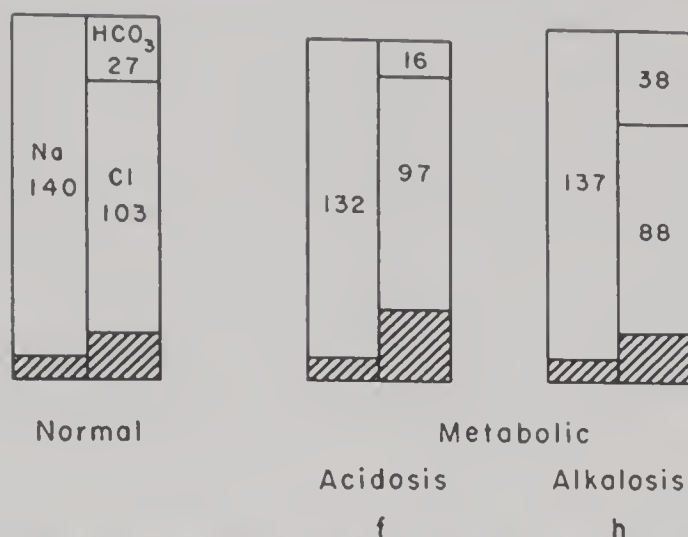


FIG. 11-8. SERUM ELECTROLYTE PATTERNS IN PRIMARY METABOLIC DISTURBANCES

The concentrations of the principal serum electrolytes are shown in cases of metabolic acidosis and alkalosis. These data are from the cases with the corresponding letters, *f* and *h*, in fig. 11-7. In *f*, a patient with uremic acidosis, the lowered total CO<sub>2</sub> and HCO<sub>3</sub><sup>-</sup> reflects the reduction of buffer anion and base due to the metabolic and renal retention of phosphates, sulfates, and organic acids, and loss of sodium. In *h*, a patient with the metabolic alkalosis of potassium deficiency due to ACTH therapy, the elevated HCO<sub>3</sub><sup>-</sup> reflects the increase in buffer anion and base due to the migration of hydrogen and sodium into cells.

interruption of the processes that have produced such depletion, and the restoration of sodium stores, become the goals of therapy. In high chloride acidosis relief of this disturbance depends upon withholding the chloride ion and allowing renal excretion to restore the level to normal. In the metabolic acidosis of diabetic acidosis and coma, therapy consists of giving insulin, saline, water, etc. which will permit restoration of the concentration of fixed ions to normal levels. In salicylate poisoning diuresis will usually suffice to remove this foreign anion, though vivodialysis via an artificial kidney (8a) has been successfully employed. In acute renal failure the most realistic hopes are those directed to restoration of kidney function toward or to normal; in chronic renal failure limited function must be supported; in either case only temporary relief is afforded by the artificial kidney. In all these conditions it may be advisable to give sodium bicarbonate or sodium lactate solution to combat the acidosis. The actual rise produced in serum CO<sub>2</sub> content or buffer base concentration will vary widely from case to case because a considerable and varying portion of the sodium administered will enter the intracellular fluid (8b). Such sodium alkali therapy must be undertaken with caution, however, because of the concomitant hazards of inducing or exacerbating hypertension or edema (see chap. 12 and Part IV).



**2. Primary metabolic alkalosis or buffer anion and base excess** may be the result of a variety of processes. These include direct loss of fixed anion (chloride) as HCl in gastric fluid removed during *vomiting* or *gastric suction* (9a-c), retention of fixed cation (sodium) due to the *excessive ingestion of alkalis* as antacids (9d, e), *congenital diarrheal loss of chloride* (9f, g), disproportionate chloride to sodium excretion by the kidney during the use of *mercurial diuretics* (9h-j), and a combination of disproportionate chloride excretion and transfer of hydrogen and sodium into cells secondary to potassium deficiency (10a-q). The experimental basis of this last phenomenon was described and documented in the preceding chapter. The pathogenesis of the potassium deficiency usually includes extrarenal loss of the ion (e.g., gastrointestinal fluid drainage), hyperadrenocortical activity (e.g., adrenocortical tumor, ACTH and DOCA administration, post-operative stress), as well as a low potassium intake. In all these types of alkalosis the buffer base is increased with a variable secondary rise in  $P_{CO_2}$  as a result of hypoventilation (fig. 11-7, g, h). The serum electrolyte pattern is characterized by a high carbon dioxide and bicarbonate content and a low level of chloride (fig. 11-8, h). The urine may be alkaline or, paradoxically, it may be acid especially during prolonged metabolic alkalosis and potassium deficiency (9e, 11a); this probably represents failure of renal tubular secretion of potassium to compete with that of hydrogen ion (1i). (See also figs. 3-15, 6-5, 13-5, 21-3, 22-1, and 23-2).

The clinical signs of metabolic alkalosis include hypoventilation, tetany, weakness, and mental confusion, as well as other evidence of the specific underlying condition. Treatment of extracellular deficit of chloride is best accomplished by giving sodium chloride solutions and permitting the kidney to excrete the relative excess of sodium. Cases complicated with potassium deficiency should receive potassium chloride or potassium chloride plus phosphate solution; some sodium is desirable in these solutions but an internal source of sodium should be recognized since excess sodium is transferred from intracellular to extracellular fluid as potassium is taken up (10p, 11b) (fig. 11-9). Ammonium chloride has been recommended (11c) but, in the opinion of the authors, has had no place in the treatment of the above types of metabolic alkalosis since the development of potassium chloride solutions; it provides none of the fixed cations which are usually needed and ammonium ion is toxic when administered above the optimal rate (11d, e). Ammonium chloride is indicated in the metabolic alkalosis due to mercurial diuresis in edematous patients and may restore sensitivity to the diuretic in patients who have become refractory (9j). A note of caution should be sounded against the administration of chloride, especially ammonium chloride, to patients with a high total  $CO_2$  and buffer base sec-

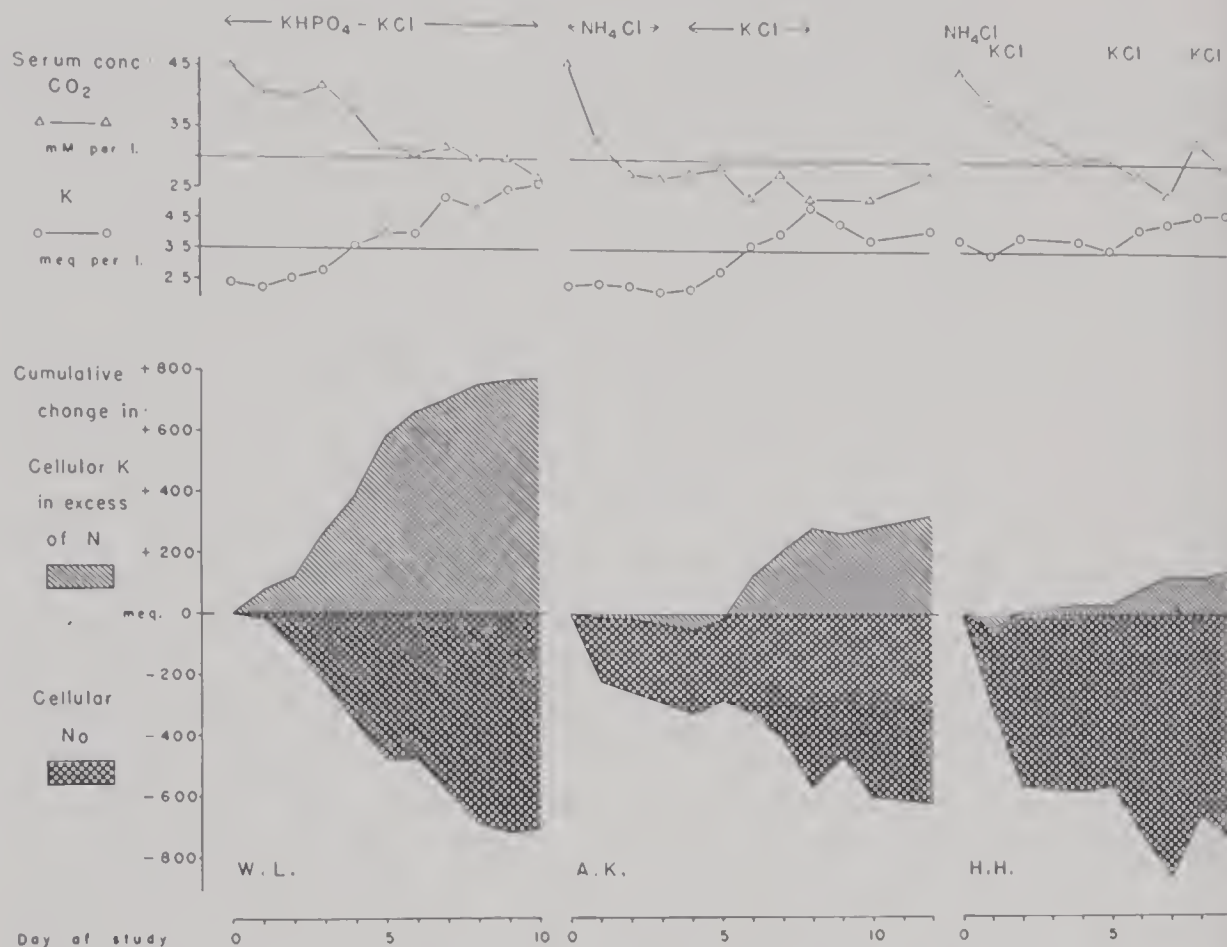


FIG. 11-9. TREATMENT OF METABOLIC ALKALOSIS: RELATION OF CHANGES IN SERUM LEVEL OF CARBON DIOXIDE AND POTASSIUM TO CUMULATIVE CHANGES IN SOME OF THE INTRACELLULAR CATIONS; THREE TYPES OF RESPONSE

In Patient W. L. (starvation, stress) intracellular potassium increased and intracellular sodium decreased simultaneously with the return of the serum  $\text{CO}_2$  and K to normal levels (balance data on this patient are given in fig. 3-15). In Patient A. K. (ulcerative colitis) during the administration of  $\text{NH}_4\text{Cl}$  the serum  $\text{CO}_2$  level returned to normal coincidently with a loss of cellular sodium (in exchange for hydrogen ion, not shown) and prior to an increase in intracellular potassium. In patient H. H. (postoperative vomiting, gastric lavage, balance data shown in fig. 6-5) the serum  $\text{CO}_2$  level returned to normal in association with a loss of intracellular sodium and without any significant subsequent uptake of cellular potassium; hydrogen ion transfers were not calculated. (From Elkinton *et al.* (10p).)

ondary to a primary respiratory acidosis; therapeutic obliteration of this compensatory response may kill the patient.

#### IV. Mixed Disturbances—Clinical

Not infrequently two primary disturbances of the anion-cation equilibrium are occurring simultaneously in the same patient. Such so-called "mixed" disturbances are illustrated in figure 11-10. Where the changes in each factor are in the opposite direction (fig. 11-10, i, j), two primary disturbances can only have occurred simultaneously. The causes of each are

usually one of those outlined above for each category. In such a combination the deviation in pH is bound to be extreme and the patient's life may be jeopardized. Mixed disturbances in the opposite direction (fig. 11-10, k, l) are clinically more common and are harder to recognize since they tend to cancel out each other's effect on the pH. Often the coexistence of two such primary alterations in acid-base equilibrium can only be identified by following the clinical and chemical course of such a patient. Such a situation is shown in figure 11-11 which also illustrates the diagnostic inadequacy, with respect to anion-cation disturbances, of serum or blood  $\text{CO}_2$  and bicarbonate concentrations alone as compared with the determination of buffer base concentration and pressure of carbon dioxide. The administration of  $\text{NaHCO}_3$  to a patient with a diabetic metabolic acidosis appeared to restore only partially on the second day the anion-cation balance as assessed in terms of whole blood  $\text{CO}_2$  content (left-hand side of diagram). In fact, at this point the buffer base was restored almost to normal, and the patient was actually alkalotic (pH = 7.55) because of a simultaneous primary stimulation of the respiratory center as shown by the low  $\text{P}_{\text{CO}_2}$  (right-hand diagram). When  $\text{NaHCO}_3$  was no longer given, the patient's pH returned

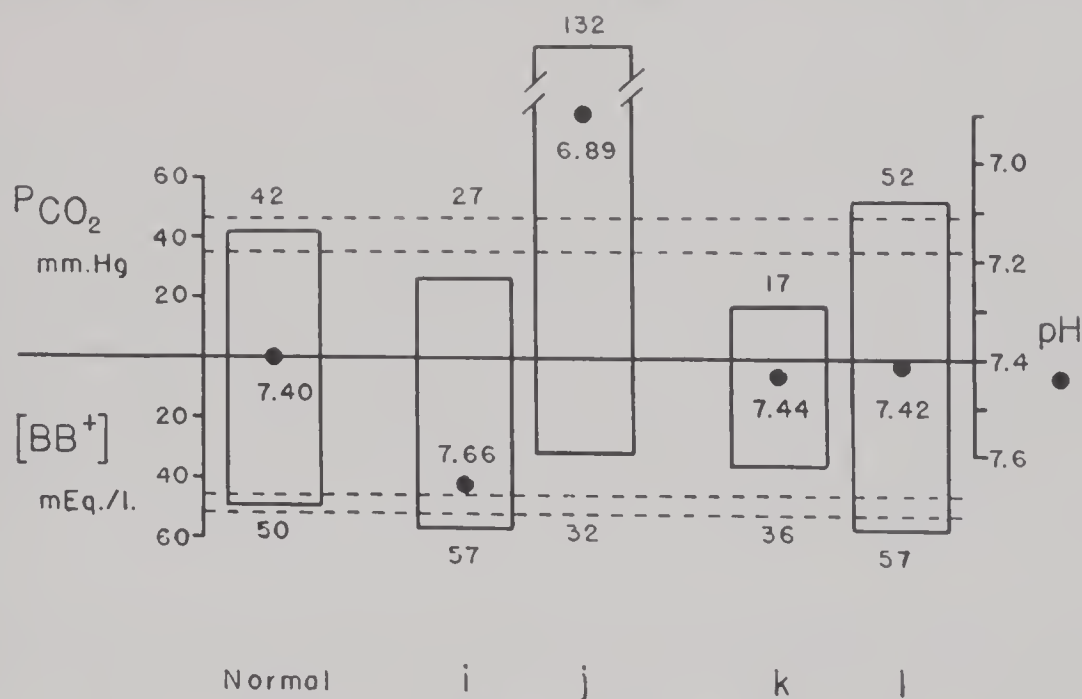


FIG. 11-10. MIXED DISTURBANCES

The data shown indicate the following combinations: a primary deficit of  $\text{CO}_2$  plus a primary excess of  $\text{BB}^+$ , or a mixed alkalosis, in a case of constrictive pericarditis with anoxia receiving mercurial therapy (i), primary retention of  $\text{CO}_2$  and primary deficit of  $\text{BB}^+$ , mixed acidosis, in a curarized mental patient given  $\text{CO}_2$  (j); primary  $\text{CO}_2$  deficit plus primary deficit of  $\text{BB}^+$  in diabetic acidosis (k); and primary  $\text{CO}_2$  excess plus excess of  $\text{BB}^+$  in congestive heart failure with mercurial therapy (l). (From studies by Singer *et al.* (1a, b) Altschule and Sulzbach (12b) and Boek *et al.* (12c).)



Diabetic acidosis complicated by primary respiratory alkalosis  
Results of alkali therapy

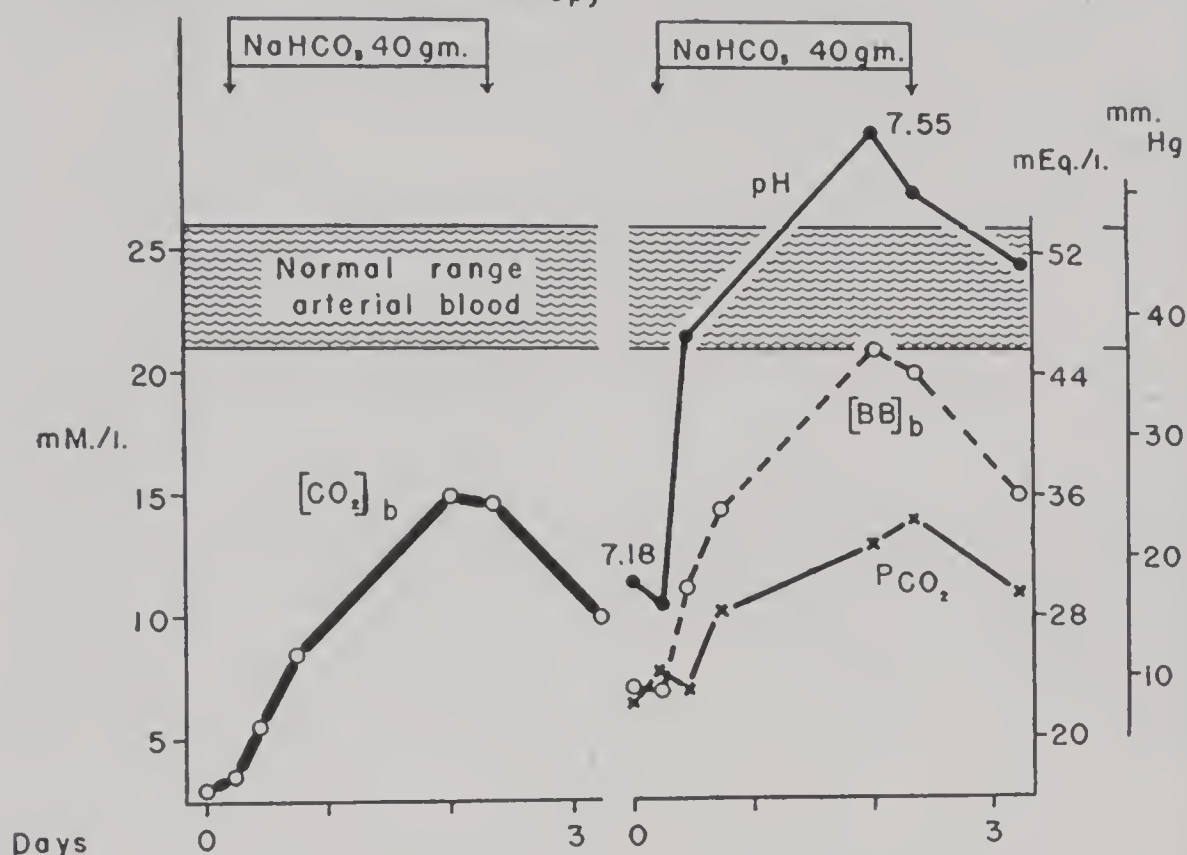


FIG. 11-11. ILLUSTRATION OF THE DIAGNOSTIC INADEQUACY OF TOTAL CO<sub>2</sub> CONTENT ALONE, COMPARED WITH DETERMINATION OF THE MAIN VARIABLES OF BUFFER BASE AND PCO<sub>2</sub>, IN A CASE OF DIABETIC ACIDOSIS TREATED WITH ALKALI

On the left-hand side, the partial rise of total CO<sub>2</sub> might be interpreted to mean that a metabolic acidosis had been only partially corrected. The precise state of acid-base equilibrium is revealed in the right-hand diagram which shows that at the end of two days the buffer base had returned to within the lower limit of normal but was associated with a primary respiratory alkalosis (low PCO<sub>2</sub> and high pH). Withdrawal of the NaHCO<sub>3</sub> therapy permitted a drop in buffer base leading to a normal pH (primary buffer base deficit plus primary CO<sub>2</sub> deficit). (Modified from Singer and Hastings (13b) and Bock *et al.* (12c).)

(on day 4) to within the normal range as the result of a mixture of primary deficits of both buffer base and carbonic acid. This mixed disturbance is also diagrammed in figure 11-10, k; the anion-cation diagnosis at this time could only be made in the light of prior clinical and chemical data.

Another clinical condition characterized by a mixture of two primary disturbances which tend to compensate each other in terms of pH is acute salicylate poisoning. Retention of the organic anion in abnormal amounts reduces the buffer anion and base, a metabolic acidosis. Usually, however, the organic acid or the severe acidosis stimulates the respiratory center resulting in primary respiratory deficit of carbonic acid. Over-vigorous treatment of the buffer base deficit may, therefore, push the pH to the

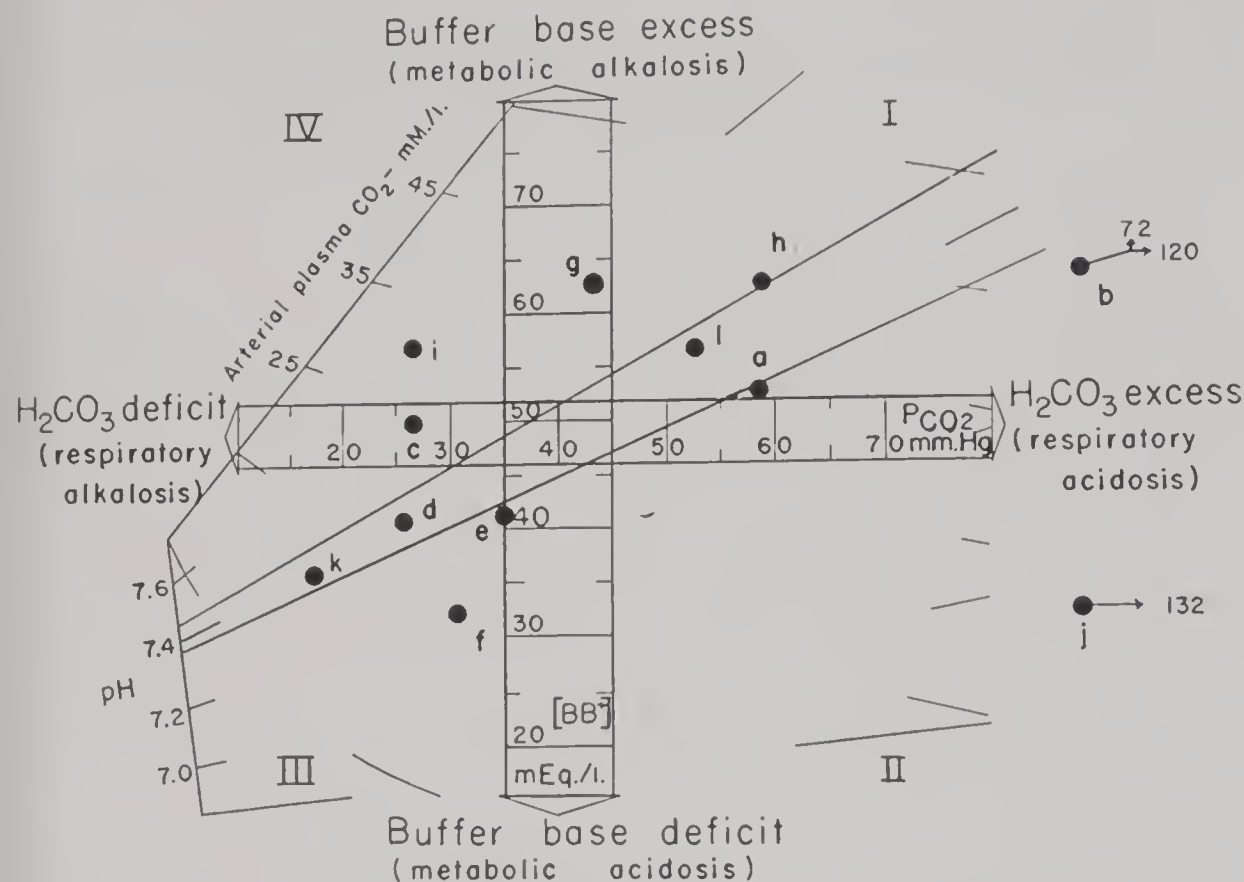


FIG. 11-12. ACID-BASE DISTURBANCES PLOTTED ON THE SINGER GRID

The various types of disturbances presented in figs. 11-4, 11-7, and 11-10, are here plotted together.

This type of graph was designed by Singer (12a) to demonstrate the relationships of the primary variables of carbonic acid and buffer base. Carbonic acid excesses lie in quadrants I and II, deficits in III and IV; buffer base excesses lie in quadrants I and IV, deficits in II and III. Any value lying in quadrants II and IV must represent therefore a primary disturbance in each variable since they exhibit the opposite of a compensatory relationship. Values in I and III may indicate either independent primary variation or changes in one variable which are secondary to the other. The interpretation rests on prior clinical and chemical data although a p<sub>H</sub> value lying outside the normal parameters may greatly assist in this interpretation.

alkaline side, just as in the case of diabetic acidosis described above (fig. 11-11). The complex anion-cation disturbances of salicylate poisoning have been delineated by Singer (4h).

Two primary metabolic disturbances also may occur concomitantly and tend to cancel each other with respect to p<sub>H</sub>. Ketosis in the vomiting infant produces one such example; another results from vomiting or gastric lavage in the patient with renal retention of phosphate (see fig. 23-2).

The graphic presentation of these various types of mixed and nonmixed anion-cation disturbances can be made in another way. Figure 11-12 shows the data of the various cases presented in figures 11-4, 11-7, and 11-10 plotted on the acid-base grid designed by Singer (12a). Although such a graph may

seem complicated at first sight, it really provides a relatively simple way to present the essential data of any type of acid-base disturbance. (Compare with the mixed disturbances in congestive heart failure, fig. 13-11).

### V. Summary of the Body's Defense Against Abnormalities in Hydrogen Ion Concentration

Experimental and clinical studies of the past few years have greatly broadened our knowledge of the regulation of anion-cation equilibrium and the hydrogen ion concentration of the body fluids. Such regulation is no longer considered in terms of blood alone as a physicochemical system. Ionic exchanges between buffer systems in a series of fluid phases have become well recognized and the integrated role of physiological adjustments of the lungs and kidneys much more adequately understood. As a consequence, a broader concept of anion-cation equilibrium has been foreshadowed in the 1952 Macy Conference on Renal Function (13a) and ably expressed by Pitts in his Harvey Lecture in 1953 (5b). Most of the experimental and clinical data on which this broader concept is based have been presented in these two chapters.

While much remains to be learned in this field, the student faced with so much information is perhaps entitled to a summarizing, albeit somewhat simplified, of these linked physicochemical and physiological reactions. This perhaps can best be done in terms of the linked transfers of cations which take place in the body's defense of neutrality. In figure 11-13 are shown those occurring in respiratory alkalosis and acidosis. The primary action (*a*) is an increased or decreased rate of excretion of hydrogen ion (as  $\text{H}_2\text{O}$  and  $\text{CO}_2$ ) through the lungs. In the former, respiratory alkalosis, the hydrogen loss is shared by the intracellular, as well as the extracellular, fluid, and the immediate buffering effect is spread throughout the fluid phases with sodium transferring into cells to replace the hydrogen. The renal adjustment is to conserve hydrogen and to reduce the "neutral salt" of the buffer systems by excreting both extracellular and intracellular fixed cations, sodium and potassium, with bicarbonate. In the case of respiratory acidosis, the reactions are in the reverse direction: the excess hydrogen being distributed immediately over the buffer systems of all phases, with sodium leaving cells as hydrogen enters; the renal adjustment is to increase the excretion of hydrogen ion and to augment the "neutral" salts of the buffer systems by conserving extracellular and intracellular cations, sodium and potassium, and excreting fixed anions with ammonium ion produced in the kidney. Each of these sets of linked physicochemical and physiological reactions minimizes the primary derangement in hydrogen ion concentration.

The corresponding sets of reactions in defense of neutrality against metabolic alkalosis and acidosis are shown in figure 11-14. The primary



alteration (a) is the "metabolic" decrease or increase of hydrogen ion by change in the proportion of fixed cation to fixed anion in the extracellular fluid. In metabolic alkalosis, this loss of hydrogen is shared with the intracellular buffers, sodium being exchanged for hydrogen across the cell boundary. The pulmonary response is to conserve hydrogen by hypoventilation. The renal response, to the extent that renal insufficiency is not involved, is to conserve hydrogen and to excrete extracellular and intracellular fixed cation, sodium and potassium, with bicarbonate. In metabolic acidosis the reactions are in the opposite direction. Excess hydrogen ion is buffered throughout the body fluids, being exchanged for sodium across the cell boundary. The pulmonary response is to increase the excretion of hydrogen with  $\text{CO}_2$  by hyperventilation. The renal response, if operative, is to excrete hydrogen and to conserve fixed cation, sodium and potassium, with bicarbonate; fixed anion is excreted with ammonium ion. These reactions, as in the case of respiratory disturbances, minimize the derangement of hydrogen ion concentration metabolically produced.

The preceding sequences of linked transfers of cations are those that take

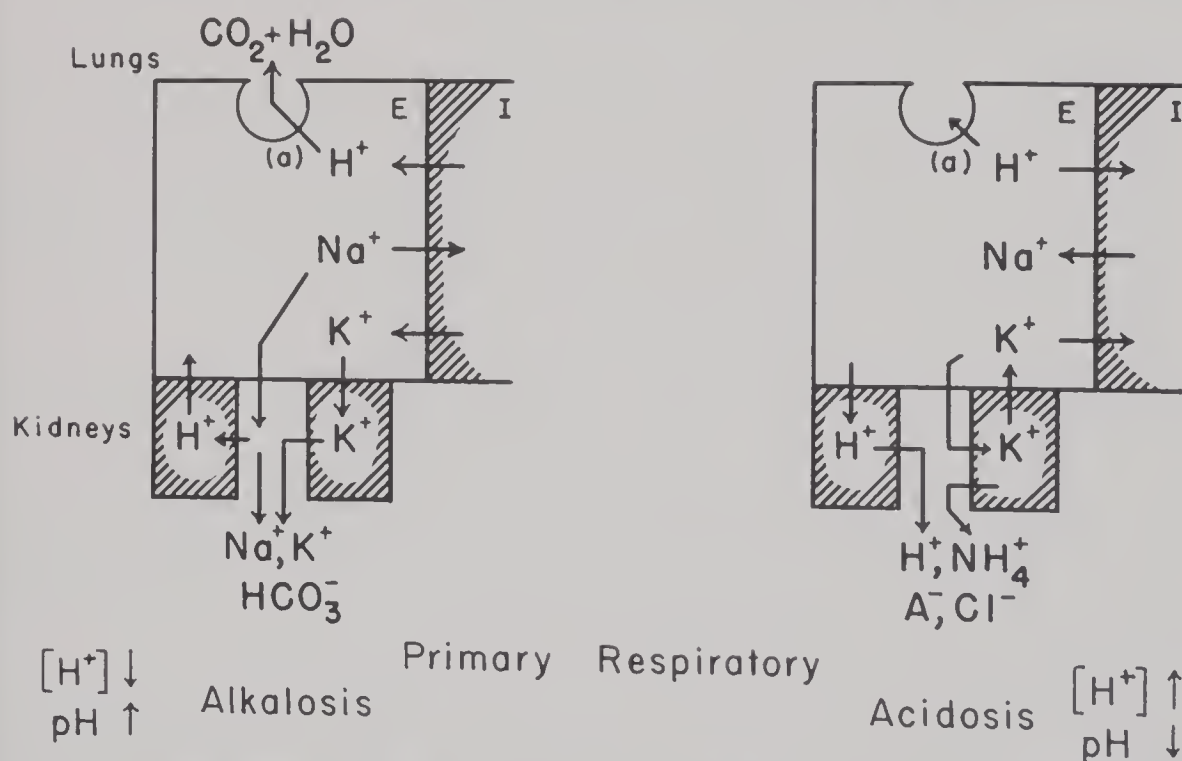


FIG. 11-13. SIMPLIFIED SCHEMA OF LINKED TRANSFERS OF CATIONS IN DEFENSE OF BODY FLUID NEUTRALITY AGAINST PRIMARY RESPIRATORY ALKALOSIS AND ACIDOSIS

E and I represent extracellular fluid and intracellular fluid, respectively. The primary disturbance is indicated at (a).

In alkalosis hydrogen ion loss is shared by the intracellular fluid, exchanging with sodium from the extracellular phase. The secondary renal response consists of inhibition of the tubular secretion of hydrogen, leading to the excretion of an alkaline urine containing potassium as well as sodium bicarbonate; this loss of potassium leads to cellular depletion of the ion. In acidosis exchanges take place in the opposite direction and an acid urine is formed.

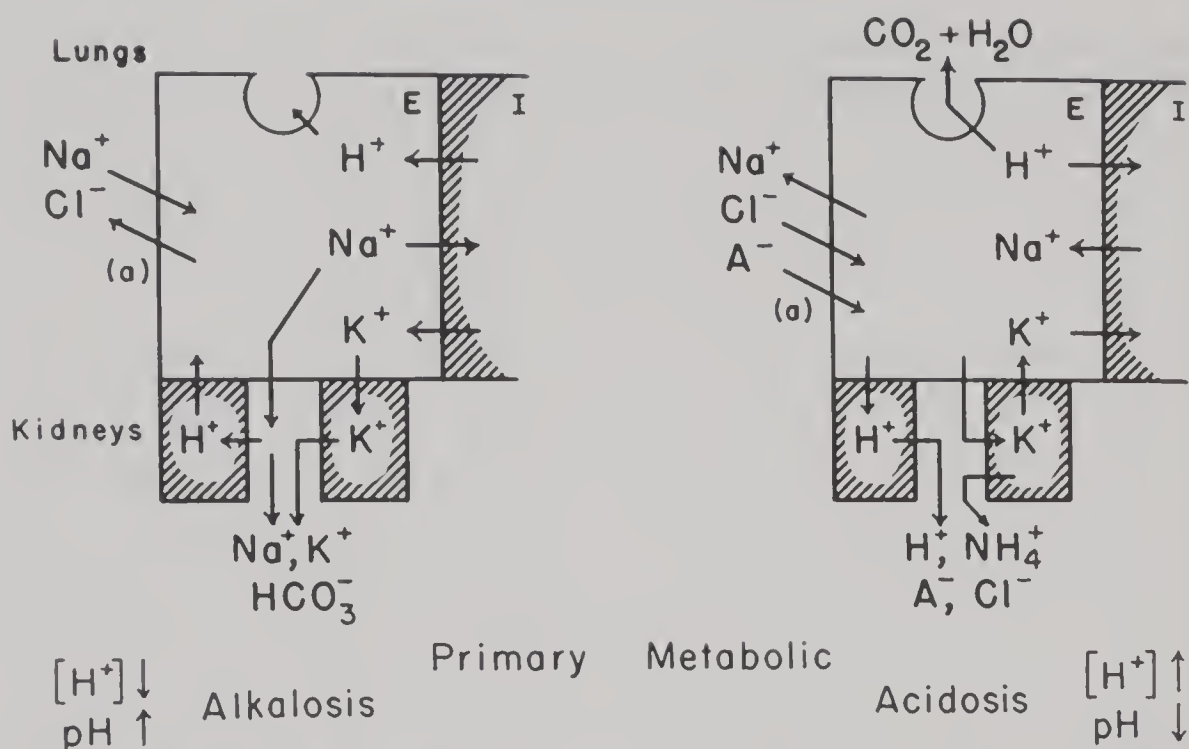


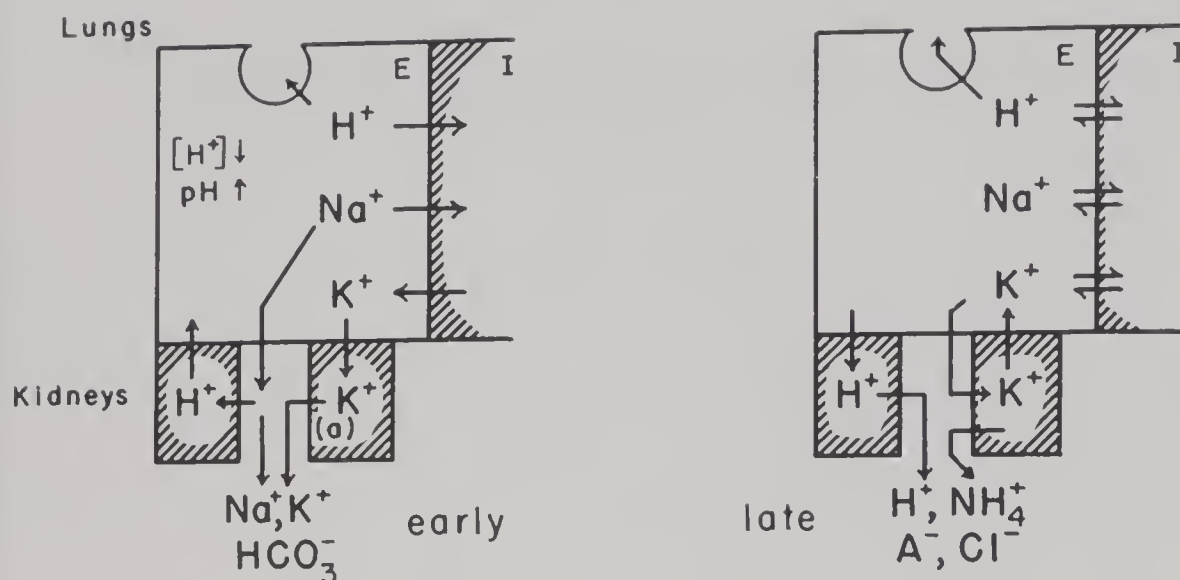
FIG. 11-14. SIMPLIFIED SCHEMA OF LINKED TRANSFERS OF CATIONS IN DEFENSE OF BODY FLUID NEUTRALITY AGAINST PRIMARY METABOLIC ALKALOSIS AND ACIDOSIS

The schema is constructed in the same manner as in fig. 11-13, the primary disturbance (a) being renal, gastro-intestinal, or metabolic.

The cationic exchanges between extra- and intracellular fluid are the same, exchanges in the kidney (unless the site of the primary dysfunction) are the same, and the compensatory pulmonary exchanges are the opposite, of those in the primary respiratory exchanges shown in fig. 11-13.

place in defense of the neutrality of the body fluids when it is threatened by respiratory and metabolic events. However, because these transfers are linked reactions, an abnormal event occurring primarily in the chain elsewhere may result in disturbing, rather than preserving, the hydrogen ion concentration. Such an event is the depletion of intracellular potassium; the result is an extracellular metabolic alkalosis. The sequence leading to this result is presented in figure 11-15.

The primary event (a) is the depletion of cellular potassium by loss through the kidney due to adrenocortical hyperactivity or tubular dysfunction and through the gastrointestinal tract, in the absence of an adequate intake of the ion. In the early stages (left-hand diagram) sodium and hydrogen transfer into cells and in the kidney the tubular secretion of hydrogen is inhibited, potassium exchanges for sodium, and bicarbonate is reabsorbed preferentially to chloride. The result is an extracellular alkalosis and possibly an intracellular acidosis. In the late stages (right-hand diagram) cellular depletion of potassium including the cells of the renal tubule leads to extreme inhibition of renal secretion and excretion of potassium



### Primary Potassium Depletion with Metabolic Alkalosis

FIG. 11-15. SIMPLIFIED SCHEMA OF LINKED TRANSFERS OF CATIONS IN PRIMARY POTASSIUM DEPLETION WHICH RESULT IN EXTRACELLULAR METABOLIC ALKALOSIS

The schema is constructed in the same manner as in figs. 11-13 and 11-14. The primary disturbance (a) is the abnormal loss of potassium from the body through the kidney or through the gastro-intestinal tract.

The early stages are shown in the left-hand figure. Although the enhanced renal tubular secretion of potassium inhibits that of hydrogen and leads to an alkaline urine, the loss of potassium from the intracellular fluid is associated with a reverse transfer of sodium and hydrogen from the extracellular fluid to a degree that results in an extracellular metabolic alkalosis. In the late stages (right-hand figure), the potassium depletion inhibits further renal tubular secretion of the ion; this results in an abnormal stimulation of hydrogen secretion and an acid urine, further exacerbating the extracellular alkalosis.

and reciprocal enhancement of the renal excretion of hydrogen in an acid urine. This aids in maintaining the established new steady state of extracellular alkalosis. Thus, a disturbance in anion-cation balance and hydrogen ion concentration is a result rather than a cause of sequential cation transfers.

**SUMMARY:** It seems quite clear at present that intracellular fluid participates in the ionic adjustments to acid-base disturbances, and that tissue cells are buffers quite as much as are bicarbonate and the proteins of plasma and red cells. In acute respiratory disturbances hydrogen appears to exchange for cellular sodium as well as with the blood buffer proteins; under such acute conditions the renal adjustments play a minor role. Regardless of what part of the non-chloride space is involved, the principle remains the same: the total regulation of body pH involves a series of



linked extracellular, intracellular, and renal ionic exchanges. This is true for the metabolic as well as for the respiratory disturbances.

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## PART III

### *Disease Entities*





“But the urine flowed much less and finally the dropsical swelling seemed to grow. . . .”

Domenica Cotugno, 1775

## *Chapter 12*

### **RENAL FAILURE**

The role of the kidney in the homeostatic regulation of body fluid steady states has repeatedly been emphasized in the preceding discussions of physiologic processes in health and disease. It is not surprising that with circulatory failure renal function becomes compromised even though the kidneys themselves are morphologically intact. It is surprising, however, to find that in many diseases of the kidneys renal function is often maintained as well as it is. Thus in some patients chronic glomerulonephritis is compatible with survival and well-being during several decades. In many instances of renal disease the compensatory adjustments that occur are so complete that no clinical disorders of water, sodium, and potassium metabolism are discernible. With inadequate compensation such changes are not only present but may be responsible for major clinical symptoms and findings. These disorders of body fluids can accelerate the course of the disease and lead to death.

In this chapter we shall concern ourselves only with renal disease accompanied by renal failure. In the discussions which follow, emphasis will be placed upon the importance of an optimistic, as well as a realistic, attitude in treating diseases of the kidneys. This view is based on two beliefs. The first is that many patients with reversible lesions and disease states involving renal failure are given up as doomed when such a prognosis is not necessarily warranted. The second belief is that the chronic renal disease of many patients is compatible with life for longer periods than is usually appreciated; these patients should be given intelligent medical guidance and care.

#### **I. Acute Renal Failure Due to Tubular Necrosis**

Abrupt suppression of kidney function characterized by oliguria or anuria can occur as a result of 1) pre-renal or circulatory failure, 2) intra-renal

damage, and 3) post-renal or urinary tract obstruction. Intra-renal lesions may be those of acute tubular necrosis, of acute glomerular nephritis, or of collagen diseases such as lupus. In this section we are concerned with the intra-renal lesions of acute tubular necrosis; other types of acute renal failure are discussed in the succeeding sections.

### *A. Etiology and Pathology*

Apart from mechanical obstructions, acute tubular necrosis is today the commonest cause of abrupt renal shutdown. First described in detail by Bywaters (1a-c) in war casualties and later given the name "lower nephron nephrosis" by Lucké (1d), it has since been reported under a variety of other names including ischemic nephrosis, tubular nephritis, glomerulonephrosis, acute toxic nephrosis, acute ischemic nephropathy, etc. The descriptive term of Bull and associates (1e) of "acute tubular necrosis" seems to the authors to be the most appropriate name for the pathological state and "acute renal failure" for the syndrome of the associated clinical and biochemical abnormalities due to this group of lesions. This syndrome recently has been the subject of a number of detailed reviews (1d, f-k).

In essence, this entity is due to extensive tubular damage produced by nephrotoxic agents such as mercuric ion or carbon tetrachloride (2a-g), by untoward reactions to drugs such as the sulfonamides (3a-c), by episodes of intravascular hemolysis such as incompatible blood transfusion or black-water fever (4a-g), or by renal anoxia due to shock and circulatory failure (5a-k). The histopathology, extensively studied by Lucké, Mallory, Oliver, and others (1d, 5f, 6a-c), is characterized by necrosis of the renal tubules. In the more severe cases destruction of the basement membrane occurs and this may result in failure of some of the tubules to regenerate and heal. With chemical intoxications the lesions are more uniformly placed in the proximal tubule, whereas those due to circulatory insufficiency and anoxia are sporadically located, may involve any portion of the nephron, and, despite the nomenclature, do not predominate in the lower nephron. Oliver has designated these two processes as "nephrotoxic" and "tubulorhexic"; in any particular case one or the other or both types of damage may be present.

### *B. Pathologic Physiology and Clinical Course*

The degree of pathologic damage and physiologic disturbance may vary widely and hence the clinical course may be short or prolonged and the clinical manifestations mild or severe. However, whether mild or extreme, the course of the disease can usually be divided into three characteristic phases: the oliguric, the early diuretic, and the late diuretic. The correlation of the urinary output and factors of renal function in these three phases (1e, 1h, 2e, 5g, 5h, 7a-c) is schematically shown in the well-known diagram

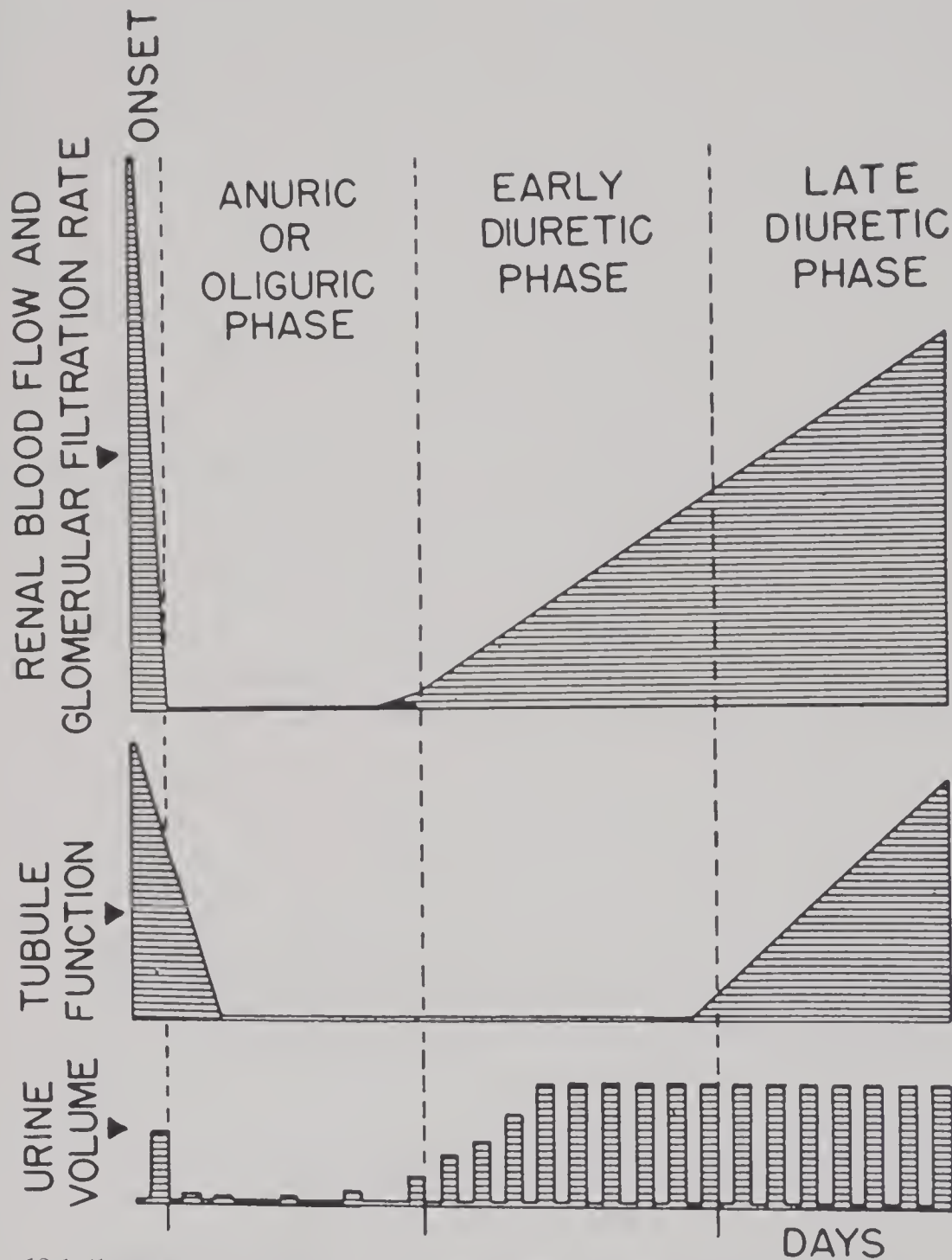


FIG. 12-1. SCHEMATIC CORRELATION OF THE RENAL FUNCTION AND URINARY VOLUME IN THE THREE PHASES OF ACUTE RENAL FAILURE DUE TO TUBULAR NECROSIS

From Bull, Joekes, and Lowe (1c)

of Bull, Joekes, and Lowe (fig. 12-1). The clinical course of these three phases is illustrated in the cases of two of our patients in figures 12-2, and 12-3.

1. The **oliguric phase** usually begins within a few hours, and is fully established by the end of the first 24 to 48 hours, after the initial insult to





to the history and physical findings are usually enough to establish the diagnosis. Occasionally, however, it may be necessary to increase carefully the total intake of water and salt to rule out a prerenal cause of oliguria (dehydration, salt depletion). Once a patient is suspected of having acute tubular damage he should be treated, until the diagnosis is disproven or recovery occurs, according to the principles outlined later in this section.

**2. The early polyuric phase** may begin with a rather abrupt increase in urinary output (fig. 12-3) or may be an acceleration of a slower steady increase begun during the earlier oliguric phase (fig. 12-2). In either case the urine volume then rapidly reaches a peak of some 3 to 6 liters. This period corresponds with the partial restoration of the renal blood flow and glomerular filtration at a time when tubular function is still minimal. The result is a dilute urine of a specific gravity approximating that of glomerular filtrate. Due to faulty tubular reabsorption this urine contains large amounts of water and extracellular electrolytes. Loss of potassium in this phase is due to high rates of tubular secretion of the ion augmenting that which is inadequately reabsorbed.

During this early polyuric phase the urea clearance remains very low

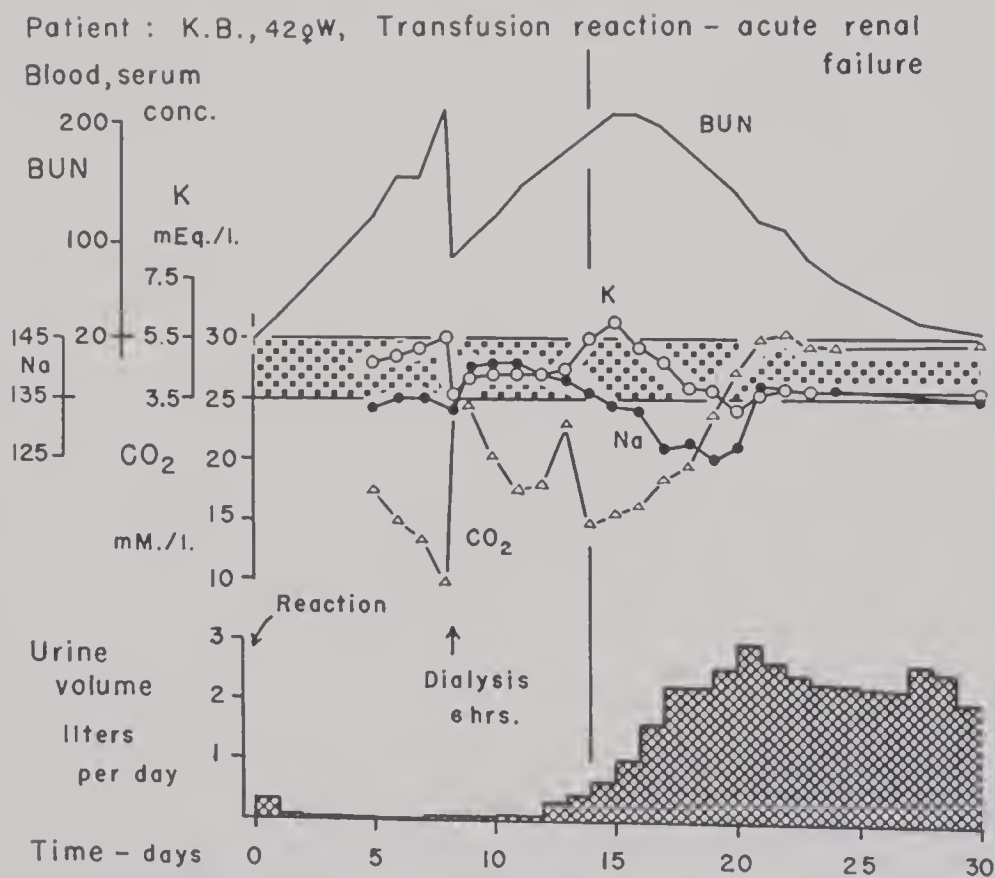


FIG. 12-3. A CASE OF ACUTE RENAL FAILURE TREATED WITH THE ARTIFICIAL KIDNEY

The clinical course and biochemical findings are shown before and after dialysis in the oliguric phase, and during the polyuric phase. In the former, treatment included adequate restriction of total fluid intake (see table 12-1). (From Bluemle *et al.* (8c, 9s).)

because of the back diffusion of urea from glomerular filtrate in the lumen through the damaged tubules as well as due to the less than optimal rate of filtration. The concentration in blood of non-protein and urea nitrogen therefore remains high or continues to rise during this period (figs. 12-2 and 12-3). Indeed, at this time the clinical signs and symptoms of uremia (stupor, twitching, hypertension, and convulsions), may reach their maximum intensity; many patients die in this phase despite the hopeful prognostic sign of a return of urine flow.

**3. The late polyuric phase** is marked by a levelling off and fall in the high urine outputs, by a decline in the clinical signs and symptoms of uremia, and by a return of the biochemical signs towards the normal range. This is the period of restoration of renal tubular function. The polyuria may take many days to subside; some evidence of renal damage frequently persists for many months or for an indefinite period, although renal function may be entirely adequate.

### *C. Body Fluid Disturbances*

In acute renal failure the abnormalities which occur in the composition and distribution of the body fluids are the direct consequence of retention in the oliguric phase and of inadequately regulated excretion in the polyuric phase. In the former phase the body fluids are essentially a closed system in which catabolism of endogenous tissue and therapy (intake) determine the body fluid pattern. In the latter stage the rapid changes which take place are the resultant of fluid constituents administered versus the renal and extra-renal losses. Although considerable variation occurs from case to case because of the multiple factors involved, the principal characteristics of these disturbances are well established.

**1. Water and total extracellular electrolyte (sodium).** The anuric patient is extremely susceptible to overhydration, a factor in therapy first emphasized by Peters *et al.* (2b) in 1933. Many patients in acute renal failure are still seen with peripheral and pulmonary edema which is primarily the result of administering fluids (to "flush out the kidneys") in amounts far beyond the capacity for extra-renal excretion through the lungs and skin. Since such fluids usually contain little or no extracellular electrolyte, the excess water is distributed between the extracellular and intracellular fluid compartments; dilution of the total body electrolyte is indicated by the associated hyponatremia (figs. 12-4, 12-5, 12-6). In addition to excessive intake the endogenous production of water by oxidation of fat and protein is a contributory factor (as discussed below in the paragraph on changes in body composition). Although the hyponatremia has been ascribed to internal shifts of sodium (7c, 8a, b), in our experience (8c, d) as well as in that of Swan and Merrill (1i) the low serum sodium



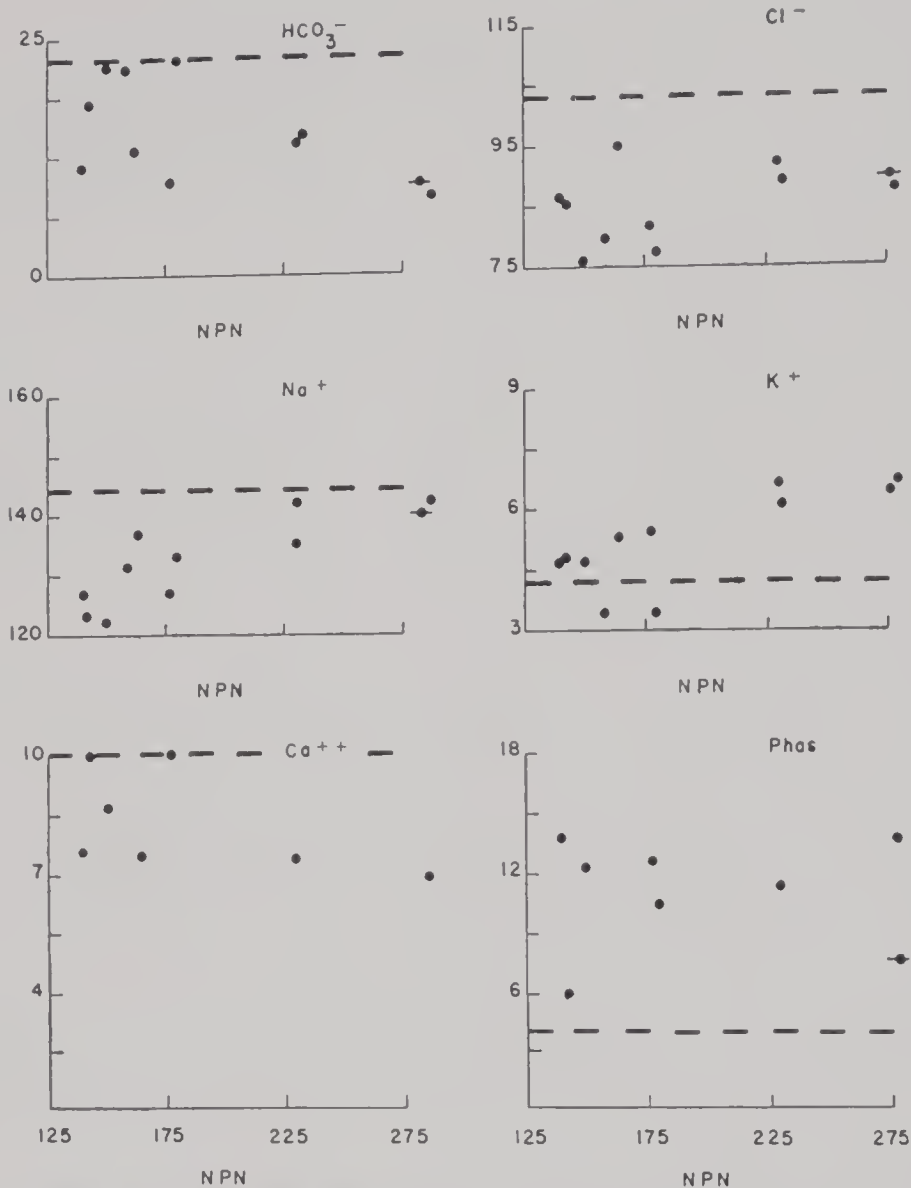


FIG. 12-4. CHANGES IN SERUM CONCENTRATION OF ELECTROLYTES IN ACUTE RENAL FAILURE

In these 10 adults and in the one child, circle with cross bar, with acute renal failure of the acute tubular damage or lower nephron nephrosis type hyperphosphatemia was regularly present with some lowering of the calcium levels. The chloride values were usually low and this was also true, with a few exceptions, of the sodium concentrations. Tendencies to acidosis and hyperkalemia are clearly discernible. (Unpublished data: F. M. Mateer and T. S. D.)

concentration is almost always a sign of overhydration. Unfortunately this is a common finding in anuric patients (figs. 12-4, 12-6, 12-7).

During the polyuric phase large amounts of water and electrolyte are excreted by the kidneys which, if not replaced in part by the therapist, will result in serious dehydration and salt depletion (1e, i, 8c). This is a relative matter since body solids as well as water are being diminished (see below and fig. 12-7). During this period hyponatremia and hypokalemia may de-

Patient I.C. Post-transfusion anuria

Therapy

Serum conc. meq. per l.

K  
O—O

CO<sub>2</sub>  
Δ--Δ

Na Balance

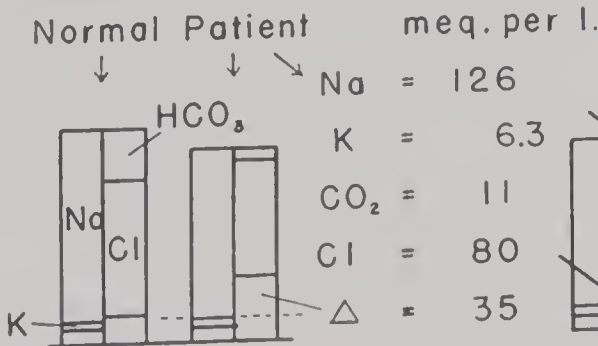
intake  
↓

output

(fecal)

Day of study

Interpretation of serum concentrations



5% gl. in H<sub>2</sub>O i.v.  
NaCl NaHCO<sub>3</sub> i.v.  
Resin

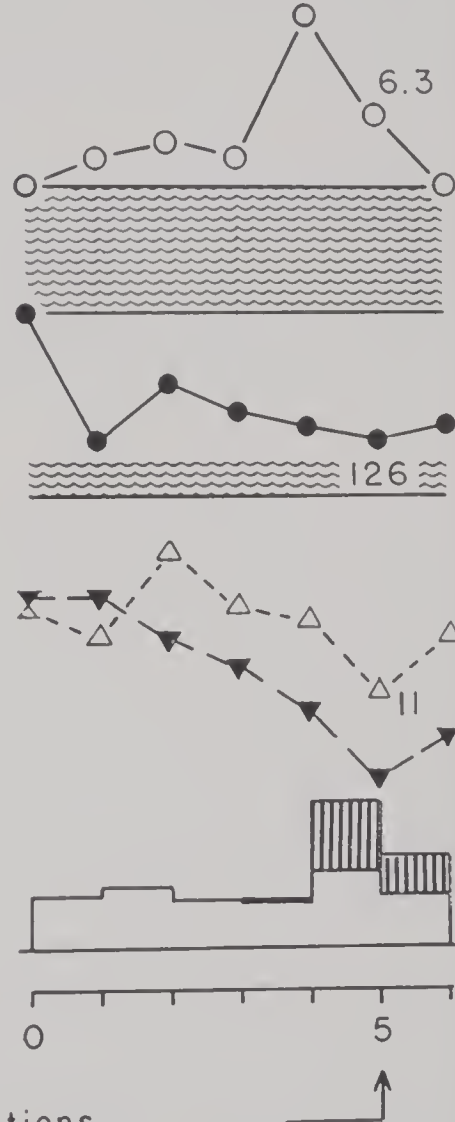
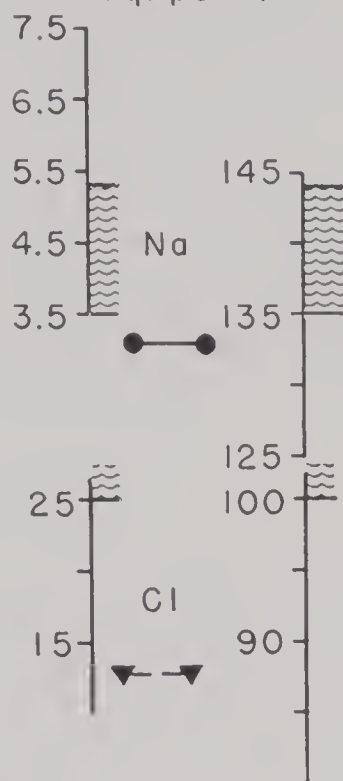


FIG. 12-5. SERUM ELECTROLYTE CONCENTRATIONS IN THE OLIGURIC PHASE: LOW SODIUM, LOW CHLORIDE, LOW CARBON DIOXIDE, HIGH POTASSIUM

Clinical data and diagnosis. I. C., a 43-year-old white female with anuria due to lower nephron nephrosis resulting from transfusion reaction, fifth to eleventh days of

velop or be present as the result of external losses of the ions rather than of overhydration and dilution (fig. 12-3).

**2. Extracellular metabolic acidosis** is the most constant derangement in body fluid structure during acute renal insufficiency. This is characterized by depression of the plasma total  $\text{CO}_2$  content, of the plasma concentrations of bicarbonate and buffer base, and of the pH of arterial blood (8e-g). It is predominantly a disturbance in relative ionic concentration (see fig. 8-5b in chapter 7), and is primarily due to the accumulation of fixed anions (phosphates, sulfates, and organic acids) from tissue catabolism (fig. 12-2 to 12-5). This increase in concentration of "undetermined anion" may routinely be quantitated as the difference between the concentration of sodium and that of  $\text{CO}_2$  or bicarbonate plus chloride (8h); it is labeled " $\Delta$ " in figure 12-5 and may be as high as 20 to 40 mEq. per liter, as compared to the top of the normal range of this moiety of 11 to 14 mEq. per liter. The mean average rate in one of our patients (8c) of accumulation of absolute amounts of "undetermined anion," is given in table 12-I.

The extracellular concentration of chloride, as measured in serum or plasma, is almost always below normal in these patients with uremic acidosis (fig. 12-4). This can usually be ascribed to overhydration although vomiting may frequently be a factor (fig. 12-5). In any case, hypochloremia is a highly desirable feature, since it indicates more "room" in the closed extracellular compartment for the steadily rising quantity of other fixed anions from cellular catabolism; it does not carry the same therapeutic significance as does hyponatremia and in general the administration of chloride ion is contraindicated in the oliguric phase. (For an exception to this rule see fig. 23-2).

During the polyuric phase and during vivo-dialysis the excess of fixed anion and the resultant metabolic acidosis are corrected (figs. 12-2, 12-3, 25-6).

**3. Potassium accumulation in extracellular fluid** is an important abnormality in respect to the patient's survival since an excess of potassium as reflected in high serum levels is known to result in cardio-toxicity,

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anuria shown on chart, treated with sodium bicarbonate given intravenously (for acidosis) and with ammonium cycle cation exchange resin by enema to remove potassium (see fig. 9-7). Total water intake restricted but somewhat exceeded the extra-renal water loss through the lungs and skin (slight degree of edema observed).

Interpretation of serum concentration on day five: *Body fluid pattern*: Excess of water in relation to sodium, despite a positive sodium balance (hyponatremia due to dilution); both extracellular and intracellular fluid volumes increased; potassium from catabolized tissue retained probably in both phases. Progressive accumulation of acid metabolites (phosphates, sulfates, organic acids) displacing bicarbonate (metabolic acidosis).

*Physiologic mechanism*: Absence of the excretory and regulatory function of the kidneys. (From Squires and Elkinton (10j).)



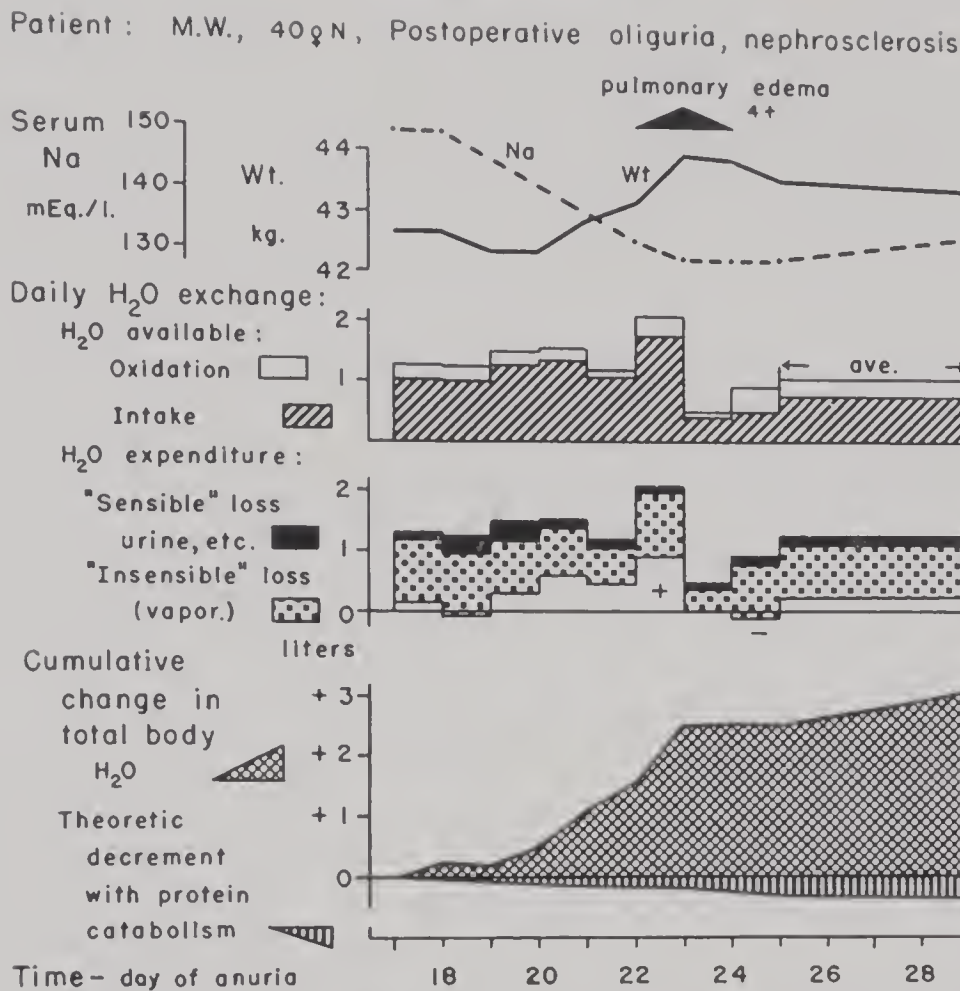


FIG. 12-6. OVERHYDRATION IN THE OLIGURIC PHASE OF A PATIENT IN ACUTE RENAL FAILURE

The increase in weight and the simultaneous decrease in serum sodium concentration are shown at the top of the chart. The daily amounts of water available are presented as the total exogenous water intake and the water of oxidation. The daily total water expenditure consists of the "sensible" loss of water in urine, feces, sweat, and vomitus and of the "insensible" loss by vaporization (calculated from the change in weight of the patient and the weights of intake and output).

The cumulative change in actual water content as compared to the theoretic change in water calculated for protein catabolism, shows that the *relative* overhydration was even greater than the *absolute* overhydration. The extra intake of 500 ml. water on the 23rd day of oliguria was given to demonstrate that the oliguria was not due to inadequate administration of water; pulmonary edema ensued. (From Bluemle Potter, and Elkinton (Sc).)

asystole, and death (8i-k). Hyperkalemia frequently occurs in renal insufficiency (8k-o), is usually associated with anuria or oliguria (fig. 12-8), and requires immediate treatment as outlined below. (See also figs. 9-8 and 9-9).

**4. Intracellular ion abnormalities** are less clearly defined. It is not known whether an intracellular excess of potassium in cardiac muscle plays a role in the cardio-toxicity mentioned above. Intracellular sodium appears

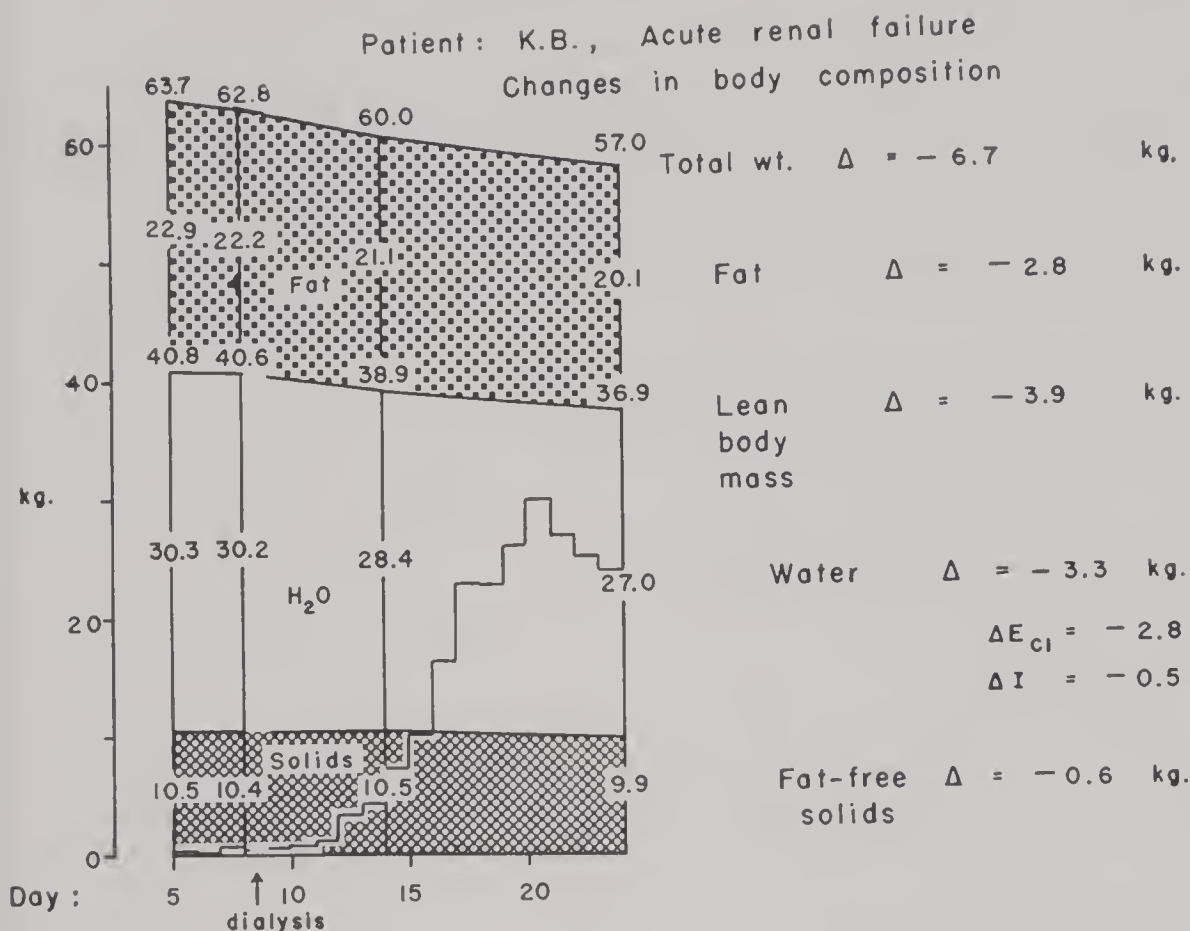


FIG. 12-7. CHANGES IN BODY COMPOSITION DURING ACUTE RENAL FAILURE

The calculated changes in the various body components are presented on the right, for the same patient shown in fig. 12-3 and in table 12-II. The absolute values are presented on the left and the outline of the daily urine volume is superimposed on a scale of 1 liter to 10 kg.

The lean body mass was calculated from the rate of production of creatinine, and the body fat by difference from the total body weight, at the end of the illness. The absolute values were then determined backwards in time using the changes in total fat and total water as calculated from the insensible weight loss, the metabolic mixture, and the change in weight. Data for the day of dialysis is omitted although the patient was essentially in balance for that 24-hour period. These absolute values for the body components are not directly measured but are indirectly derived and therefore are only approximations.

During both the oliguric and polyuric phases there was a progressive diminution in all components. (From Bluemle, Potter, and Elkinton (8c).)

to be depleted in metabolic acidosis (8p) and certainly a considerable portion of administered sodium ion leaves the extracellular fluid or chloride space in uremic acidosis (8g).

**5. Changes in body composition** during the course of acute renal failure are large and therapeutically significant. All these patients lose weight, if not during the oliguric phase, at least during the polyuric phase. Part of this weight loss is due to the combustion of body fat. The lean body mass is also reduced: a portion of the fat-free solids, which essentially is

TABLE 12-I.

INDICES OF CATABOLIC RATE, METABOLIC MIXTURE, AND FACTORS OF WATER EXCHANGE DURING ACUTE RENAL FAILURE*			
Average values in patient K.B. (Bluehle, Potter, and Elkinton(8c))			
	Unit /day	Oliguric phase (8 days)	Polyuric phase (10 days)
I. Blood and serum concentrations:			
A. $\Delta$ BUN	mg. %	+ 24.4	- 13.2
B. $\Delta$ Creatinine	mg. %	+ 2.2	- 1.8
C. $\Delta$ K	mEq./l.	+ 0.16	0
D. $\Delta$ Na -(CO <sub>2</sub> + Cl) or $\Delta$ X	mEq./l.	+ 2.3	0
II. Extracellular quantity:			
A. $\Delta$ H <sub>2</sub> O <sub>E</sub> or $\Delta$ E <sub>Cl</sub>	ml.	-100	-200
B. $\Delta$ X <sub>E</sub>	mEq.	+ 16.4	- 17.6
C. $\Delta$ K <sub>E</sub>	mEq.	+ 2.1	- 2.3
III. Total body quantity:			
A. $\Delta$ Weight	gram	-483	-298
B. Protein metabolized	gram	45	53
C. Carbohydrate metabolized	gram	86	198
D. Fat metabolized	gram	241	101
E. Total calories	ml.	2778	1980
F. $\Delta$ Water	ml.	-231	-143
IV. Water exchange:			
A. Exogenous intake	ml.	911	2525
B. Endogenous H <sub>2</sub> O of oxidation	ml.	327	249
C. Endogenous tissue H <sub>2</sub> O	ml.	136	160
D. "Sensible" H <sub>2</sub> O loss (urine, feces, etc.)	ml.	337	2233
E. "Insensible" H <sub>2</sub> O loss (vapor and sweat)	ml.	1164	889
F. Exogenous H <sub>2</sub> O needed in excess of "sensible" loss, E -(B+)	ml.	693	480
G. Exogenous H <sub>2</sub> O given in excess of "sensible" loss, A - D	ml.	574	292
H. H <sub>2</sub> O excess or deficit over "Ideal" H <sub>2</sub> O content, F - 9	ml.	-119	-188

\* + indicates excesses  
 - indicates deficits

tissue protein, is catabolized and the corresponding tissue water excreted. These changes are illustrated in figure 12-7; and the changes calculated in our series (8c) are in approximate agreement with those found in a few cases by Swan and Merrill (1i) and Moore *et al.* (8r), and in the 10 cases observed by Hamburger and Richet (8q).

The catabolism of body fat and of tissue protein results in the endogenous formation of water (1.07 ml. H<sub>2</sub>O per 1 gm. fat, 0.41 ml. H<sub>2</sub>O per gm. protein), usually called the "water of oxidation." In addition, a moiety of "tissue water" is "freed" as the normal ratio is maintained between water and the diminishing fat-free solids (or tissue protein) of the lean body mass.



Together these two sources of “endogenous water” may be equivalent to one-third or more of the extra-renal or “insensible” water loss. This has an important bearing on therapy. During the oliguric phase more water from exogenous sources is usually supplied than is required to meet the sum of the small “sensible” losses of water in urine, feces, sweat, or vomitus and the “insensible” losses by vaporization. The result is over-hydration or an increase in body water in relation to body solids, with the usual signs of edema and hyponatremia.

These factors in the water exchange of the patient whose case is illustrated in figures 12-3 and 12-7 are presented in table 12-I. The average rates of exchange are given for the oliguric and for the polyuric phases. In the oli-

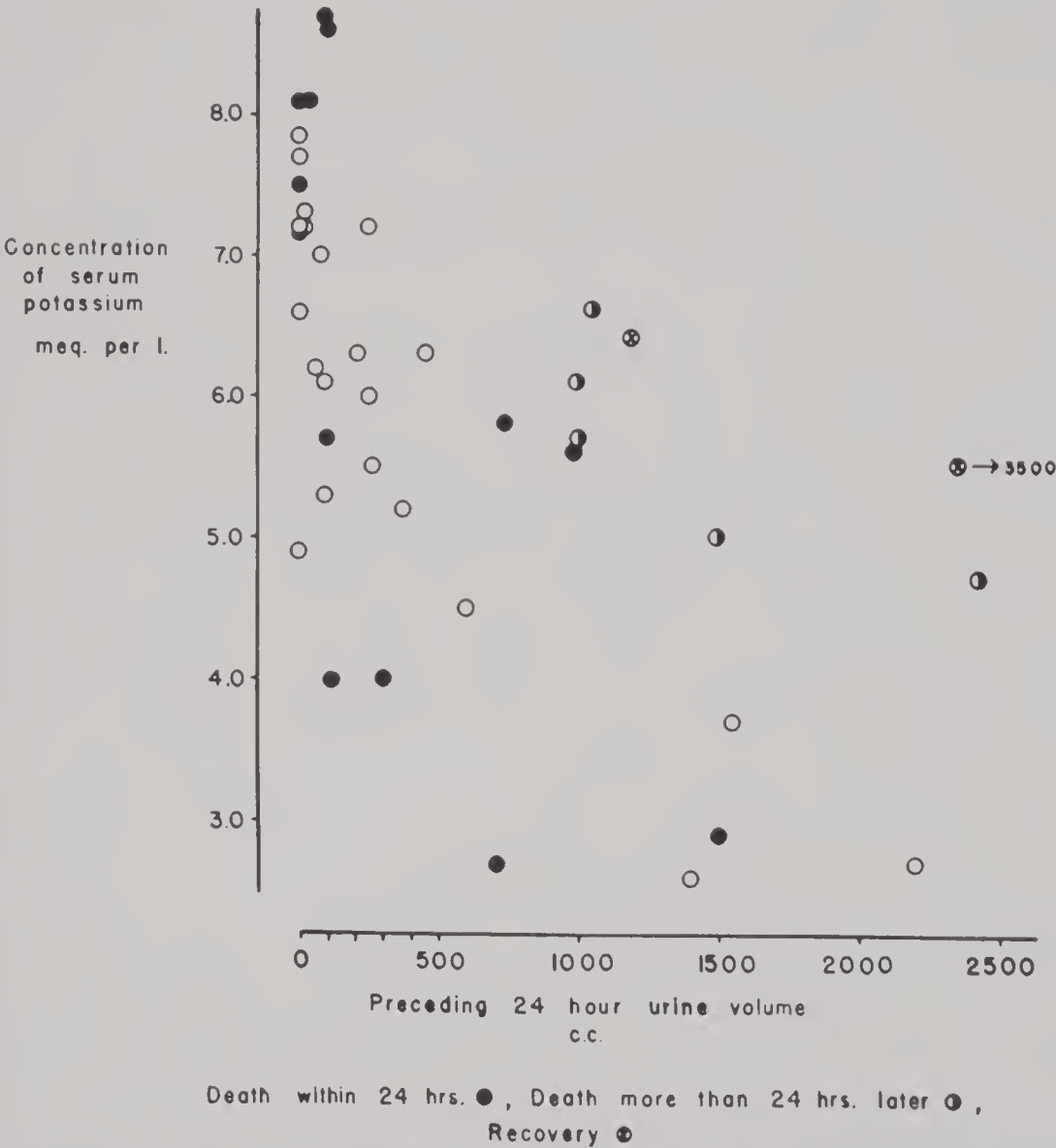


FIG. 12-8. RELATION OF THE SERUM CONCENTRATION OF POTASSIUM TO URINARY OUTPUT IN RENAL FAILURE

The data are plotted for 26 patients with acute and chronic renal insufficiency. Hyperkalemia is clearly correlated with oliguria. (From Elkinton, Tarail, and Peters (8k).) (see also Fig. 9-9).

guria phase the exogenous water supplied (IV 9), 574 ml. per day, did not exceed the exogenous water required in excess of the "sensible" water loss (IV F), 693 ml. per day; the result was that the patient did not become over-hydrated (fig. 12-7) and did not develop edema and hyponatremia (fig. 12-3). Where water is given in excess of the "sensible" and "insensible" losses without regard to the water made available endogenously, edema and hyponatremia ensue (fig. 12-6).

#### *D. Therapy in the Oliguric Phase*

The basic principles of fluid therapy of the subject with absent renal function were early emphasized by Peters *et al.* (2b) and have since been widely recognized and applied in this condition (4g, 5g, 7c, 9a-p).

**1. Rigid restriction of total fluid intake** is the cornerstone of good conservative management. The chief exception to this rule is the administration of several liters of fluid on the first day of oliguria if a nephrotoxic agent has been ingested or if dehydration is suspected as the cause of the low urine volume. To minimize tubular damage, tubular urine should be kept dilute in the presence of nephrotoxic agents and free hemoglobin. Otherwise it is of the utmost importance to restrict the total fluid intake to an amount equivalent to, or less than, the expected extrarenal loss of water. This amounts to 800 to 1500 ml. in the average sized afebrile adult patient. Since water is being formed endogenously, it may be advisable to give less. Daily weighings of the patient (9q) are of great assistance in determining total fluid requirements. Ideally, the patient should be so regulated as to lose a small amount of weight daily as both the water and solid phases of his lean body mass are diminished by the catabolic process (see above).

These patients are extremely susceptible to water overloading. If pulmonary or peripheral edema has appeared, the daily fluid intake should be reduced toward or to the zero mark; this measure alone may clear the edema (fig. 12-6). However, digitalis should be given with caution (see below) when congestive heart failure is superimposed on acute renal disease (9r, y); other measures such as oxygen therapy and aerosol sprays may be useful therapeutic adjuncts. The removal of edema fluid by ultrafiltration in a rigid dialyzer of the Skeggs-Leonards type has been accomplished by ourselves (9s) and by others (9t, u), (see chapter 25 and figure 25-7). Over-hydration is not the sole cause of pulmonary edema in anuric patients, since it can also develop as a result of a redistribution of body fluids into the pulmonary circuit.

**2. Prevention of any intake of potassium and protein** is likewise essential. *Potassium* should be allowed only under the rare circumstance of the simultaneous presence of potassium deficiency; otherwise it is contraindicated. The rise of the extracellular concentration of potassium to

dangerous levels (above 6.0 mEq. per liter) can be detected by plasma or serum determinations and can be assessed functionally by serial electrocardiographic tracings (see fig. 9-8). Treatment advocated in the past has been administration of, *a*) glucose and insulin to promote intracellular uptake of the ion, *b*) hypertonic sodium solution, and *c*) calcium as an ionic antagonist in the heart. In our experience the effect of these measures has proven inadequate and of short duration. *Vivo*-dialysis by means of an artificial kidney is the most effective and rapid treatment (see chapter 25); where this procedure is not readily available, cation exchange resin should be tried. This procedure was first demonstrated in one of our departments (9v) and has been found to be a simple and usually effective treatment of this complication (see chapter 9 and figure 9-7) (5j, 9w). Resin in the ammonium, hydrogen, or (preferably) sodium cycle is given by mouth or by enema; the latter procedure consists of the instillation through a high rectal tube of 25 to 40 grams of resin as a 10 per cent suspension in tap water, and is indicated in the vomiting patient. Occasionally, difficulties are encountered in the formation of impactions or in inability to retain the enema.

*Protein* foods are contraindicated since they will add to the catabolic products (non-protein nitrogen, phosphates, and sulfates) already being accumulated.

**3. A diet high in carbohydrate, fat, and calories** is advocated by many (9e, i, p) although Swan and Merrill (1i) doubt its efficacy in retarding the catabolic rate. Such a diet which must simultaneously be low in potassium and total fluid volume is best administered in the form of a vegetable oil mixed with sugar (see chapter 24, table 24-I, Preparation A, 9). This preparation can be dripped through a fine polyvinyl tube into the stomach in those patients in whom nausea and vomiting prevent taking a diet by mouth. For those who can eat, steamed rice with liberal amounts of butter and sugar provides a similar food. While it is unlikely that most patients will take enough calories by these regimens to approach the total caloric expenditure, the catabolism of endogenous fat and protein is probably spared to some extent and to the patient's benefit.

**4. Sodium alkali solutions for the metabolic acidosis** of uremia have proven effective (8g, 9x), although large and variable portions of the administered sodium may enter the "intracellular" or non-chloride space (8g). Opinions differ as to the advisability or magnitude of such therapy. In the authors' experience it has appeared to be life-saving in cases with severe degrees of uremic acidosis. In general, 40 to 80 mEq. of either sodium bicarbonate or sodium lactate can be infused per day by adding 1 to 2 ampules of the concentrated solution to other intravenous fluids (see chapter 24 and table 24-II, solution D, 4). It must be remembered that the deficit



of extracellular bicarbonate and buffer anion in renal failure is primarily the result of a retention of fixed anion rather than of a deficit of fixed cation. For this reason sodium alkali must be given in moderate doses in order not to overload the extracellular fluid. In the oliguric phase it is not desirable to attempt to bring the bicarbonate concentration all the way back to normal levels, unless retained fixed anion is removed by a dialyzing procedure.

The main contraindications to the administration of sodium alkali solutions are the development of hypertension, convulsions, and/or congestive heart failure. Measurement of the blood pressure and auscultation of lung bases are the best guides to this therapy. With these limitations in mind these solutions may often aid in controlling the acidosis, particularly in patients with hyponatremia (fig. 12-5).

**5. Calcium** is an important adjunct to therapy. Although the muscular twitchings and convulsions so commonly seen in uremic patients are frequently due to intracranial vascular disease and edema (10a), they may sometimes be tetanic in origin. In such cases intravenous administration of calcium ion (as 1 to 3 grams of calcium gluconate in 10 per cent solution, per day) will often control the neuromuscular irritability; occasionally as high a dose as 12 grams per day may be required to control severe convulsions. Magnesium sulfate (2 per cent solution) has been advocated (10b) but is probably hazardous in the severely oliguric patient.

Other indications for calcium are a) the intravenous administration of sodium bicarbonate or lactate, b) hyperkalemia, and c) hypocalcemia in the polyuric phase. The rationale is based on the fact that a rise in pH will induce tetany, presumably because of the decrease in concentration of ionized calcium in plasma. The use of calcium as an ionic antagonist to potassium has been discussed above. Tetany due to excessive loss during diuresis obviously requires calcium therapy (10c).

**6. The use of digitalis** in the oliguric phase presents a serious dilemma. Many such patients have potential or actual congestive heart failure and need the benefit of digitalization. On the other hand, the effect of digitalis on the heart is inhibited by high levels of potassium (10d, e), hence the abrupt removal of potassium either by dialysis or by diuresis may lead to digitalis intoxication in the patient whose digitalization was optimal when in the hyperkalemic state. This has been demonstrated experimentally by the dialysis of digitalized dogs (10f). Since calcium antagonizes potassium and enhances the effect of digitalis in the heart (10d), it is clear that each patient presents an individual problem in respect to the simultaneous variation of these three physiologic and therapeutic factors.

**7. Vivo-dialysis** of the patient with acute renal failure has been accomplished by peritoneal and gastro-intestinal lavage, by exanguination trans-

fusion, and by extra-corporeal hemodialysis in artificial kidneys of the various types developed by Kolff, Alwall, and Skeggs and Leonards. Although the efficacy of dialyzing procedures in reducing mortality has yet to be settled, in the authors' opinion this procedure is indicated, and may be life-saving, in those patients with a high catabolic rate due to infection, trauma, etc. The indications, technics, and hazards of vivo-dialysis are discussed in detail in chapter 25.

**8. Other procedures** such as decapsulation of the kidney and the injection of procaine have been recommended for acute tubular necrosis (10g, h). We see no need for their use in place of the preceding measures of therapy.

### *E. Therapy in the Polyuric Phase*

The guiding principle of treatment in this phase of the disease is to replace the excessive amounts of water, extracellular electrolytes, and potassium being lost through the diuresing kidney. In determining the amount of these constituents to administer each day the following items of information are helpful: 1) the daily decrement of weight, 2) the presence or absence of hyponatremia or hypokalemia, 3) the amount of water and electrolyte excreted the previous day, 4) electrocardiographic evidence for or against hypokalemia, and 5) the clinical appearance of the patient in respect to lethargy, thirst, and signs of hypotension and peripheral vascular collapse. Restriction of water may slightly diminish but will not retard the diuresis (1i, 10i), since the diuresis is due to faulty tubular reabsorption and not just to over-hydration during the oliguric phase. During the height of severe diureses the rapid development of fluid depletion should be watched for closely and, if possible, prevented by administration of adequate amounts of electrolytes and water.

Finally, it should be emphasized that as soon as the azotemia subsides (late polyuric phase) it is important to place the patient in an anabolic state by giving a high protein diet.

## **II. Other Forms of Acute Renal Failure**

Other intra-renal lesions besides tubular necrosis, as well as pre-renal and post-renal conditions, may cause acute failure of the kidneys. In general, the effects on the body fluids are similar to those just presented and will therefore not be discussed again in detail. Certain therapeutic features, however, are different and warrant some mention.

### *A. Acute Glomerulo-, Pyelo- or Focal Nephritis*

Manifest renal failure appears much more frequently in glomerulonephritis than it does in pyelonephritis. It is questionable whether focal

nephritis by itself can impair renal function sufficiently to produce renal failure. In other respects, however, these three entities tend to produce a common picture which varies only in degree. Thus hypertension, albuminuria, casts, erythrocytes and leukocytes appear in all, apart from the evidences of infection, systemic and urinary, in pyelo- and in focal nephritis. The bacteriologic component in these last two entities immediately indicates that prompt and successful therapy of the infection and of the underlying cause will usually restore renal function to its former levels.

The antibiotic-chemotherapeutic approach is of limited value, if any, in glomerulonephritis where infections, usually of the respiratory type, serve only as incitants of the nephritic reaction. Clinical observations suggest that many of the cases of acute glomerulonephritis subside and resolve spontaneously (11a-g). It is therefore very difficult to estimate the actual percentage of renal failure in acute glomerulonephritis. Obviously, hospital admission statistics will be based largely on the more severe cases. Nonetheless these are the problem cases and hence the discussion of renal failure will be limited to these.

**1. Clinical and laboratory manifestations in acute glomerulonephritis.** In the acute phase the malaise, anorexia, headache and weight gain which appear in many of the patients are accompanied by hypertension, diminished urine volumes, and edema. Indeed, congestive heart failure is a frequent and dangerous concomitant of acute glomerulonephritis (9y, 11h). Convulsions develop in a few patients. In the early phase of acute glomerulonephritis of sufficient severity to require hospitalization the whole blood non-protein nitrogen is slightly or moderately elevated, and hypoalbuminemia and hyperchloremia are often present. Sodium, potassium, and serum inorganic phosphorus may be elevated. On the other hand serum carbon dioxide content and the globulin and calcium levels are usually not altered.

In many of these patients improvement and apparently complete recovery occur spontaneously during enforced rest, digitalization, sodium restriction, etc. This may require many months. Occasional patients with acute glomerulonephritis go on to complete anuria. Some of these represent instances of cortical necrosis (11i). In either case the prognosis is grave with potassium intoxication, pulmonary edema, convulsions, respiratory failure, and death, as in acute tubular necrosis. The therapy of these patients is the same as that outlined for anuric patients with that disease.

*B. Acute Renal Failure in Disseminated Lupus, Rheumatic Fever, and Other Collagen Diseases*

Occasional patients with these disease entities show particular renal involvement with rapidly progressive failure (11j, k). If the course of the



disease cannot be retarded by adrenocortical steroids or ACTH in adequate dosage, the only measure left is vivo-dialysis. We have been only partially successful in treating such patients by conservative means or by vivo-dialysis (8g, 9s, 111).

### *C. Pre-renal (Circulatory) Acute Renal Failure*

This category of acute renal failure includes those patients with intact renal tubules who fail to make urine because of an inadequate renal blood flow and rate of glomerular filtration. This is failure of the whole renal circulation and not an intra-renal shunt of blood from cortex to medulla, as described by Trueta *et al.* in experimental animals (11m). The Trueta shunt has not been found in human subjects (1e, 11n). Pre-renal circulatory failure is probably one of the commonest types of acute renal insufficiency; it is recognized by the prompt restoration of urine flow and renal function when the circulatory inadequacy has been treated. Such inadequacy of the general and renal circulation is not infrequently the consequence of sodium depletion in patients with hypertension or congestive heart failure who have received prolonged treatment with low sodium diets and mercurial diuretics. A similar episode may occur in the postoperative patient whose deficits of extracellular electrolyte have not been adequately replaced. Despite the possibility of some increase in localized or generalized edema or in hypertension, such patients should be given a trial increase in sodium intake (see chapter 23). Patients with severe shock, of course, may develop tubular necrosis, as described earlier in this chapter.

### *D. Post-renal Obstruction as Cause of Acute Renal Failure*

These cases properly belong in the realm of urology but they are mentioned here because the question of obstruction as a cause of anuria or renal failure must be raised in each patient (11o). This especially is true in those patients who present *complete* anuria as opposed to severe oliguria (9s). Patency of urinary passages must be established in each patient by ureteral catheterization or other means. No amount of fluid therapy or dialysis can by itself remove an obstruction caused by a bladder or pelvic tumor, or by an inadvertent ligature, though these measures will serve to tide the patient over until the obstruction can be removed.

## **III. The Nephrotic Syndrome and Renal Failure**

The nephrotic syndrome in its essence consists of profuse albuminuria which ultimately depletes serum albumin and may result in edema or anasarca. In adults it is seen most often as a phase of glomerulonephritis, though it may also occur in amyloidosis, in syphilis, in diabetes mellitus as the Kimmelstiel-Wilson syndrome, in disseminated lupus, or as a reac-

tion to therapy with certain anticonvulsive drugs. In all of these instances some measure of hematuria and cast formation is present. The occurrence of lipid nephrosis in children, characterized by profuse albuminuria without formed elements and without vascular reaction, was originally responsible for the concept that this was a metabolic rather than a renal disorder (12a-e). The better prognosis in children with this disease compared to adults with a nephrotic component was thought to support this view. In recent years, however, closer study of the cases of pure lipid nephrosis has revealed hypertension as well as findings compatible with a glomerulonephritis often enough to warrant including this entity within the nephritic group. The nephrotic syndrome also may be a manifestation of renal vein thrombosis. The clinicopathologic meaning of the nephrotic syndrome has been reviewed by Allen (12f).

Many of the children and adults with the nephrotic syndrome have an elevation of the whole blood non-protein nitrogen when first seen, in addition to the characteristic hypoalbuminemia and the frequent hypercholesterolemia. More detailed studies of renal blood flow and glomerular filtration point to the presence of renal disease with compensating adjustments (12e). Usually, these ultimately prove inadequate to cope with ordinary solute and water loads, and retention of sodium, chloride, and water results, and metabolic acidosis develops.

The treatment of the above manifestations has been detailed in chapter 9. Particular care should be paid to the sections dealing with the use of colloid solutions and with the administration of potassium. The only regimens which may prove effective in the treatment of the nephrotic syndrome are a) the administration of cortisone or ACTH in adequate dosage to those patients in whom the underlying disease is either glomerulonephritis or lupus, and b) the removal of the cause whether it be amyloidosis, syphilis, or a drug which is producing a toxic reaction (13a-o). It should be pointed out, however, that patients with far-advanced renal failure have not responded favorably to ACTH or cortisone and hence these agents should be given in the early stages of renal failure. In children, remissions of the nephrotic syndrome may follow acute exanthematous diseases such as measles. There is at present no specific treatment and only symptomatic relief for patients with the Kimmelstiel-Wilson syndrome.

#### **IV. Chronic Renal Failure**

##### *A. Functional Characteristics*

Progressive renal damage gradually reduces the amount of functioning parenchyma. This occurs in the course of glomerulo- or pyelonephritis, in nephrosclerosis, in congenital polycystic disease, in obstructive urinary tract lesions, in primary hyperparathyroidism, in vitamin D poisoning as

well as in certain cases of gout and of collagen disease (11j, k, o, 14a-i). In all of these entities manifest renal failure is often staved off by compensatory mechanisms. Thus the decrease in the number of functioning nephrons results in hypertrophy of the remainder; decreases in blood flow to the kidney are in part or largely cancelled by the increased percentage of the blood converted to filtrate; rises in urea nitrogen increase the clearance of this material; and an increased intake of water and output of urine permit solute excretion in a kidney with limited concentrating and diluting abilities (14f, i).

When such compensating mechanisms are no longer adequate manifest renal failure appears. Its subsequent course is usually gradual and in many patients compatible with effective living over a period of decades. Whenever an accelerated decline appears in such patients a search must be made for the precipitating or inciting cause: did a respiratory, urinary, or systemic infection produce an acute flare-up; has the patient developed congestive heart failure; or has dehydration or salt depletion been superimposed upon the chronic limitations of kidney function, etc.?

### *B. Electrolyte Abnormalities*

The picture of ultimate far-advanced renal failure or uremia is well-known clinically, although many of the biochemical changes are not fully appreciated. The rises in urea, creatinine, uric acid and other components of the non-protein nitrogen, as well as in the undetermined acid fraction, are accompanied by a progressive decline in serum total carbon dioxide content. This metabolic acidosis does not produce any recognized symptoms until the bicarbonate level is below ten milliequivalents per liter, when overbreathing of the Kussmaul type may set in. Characteristically the serum inorganic phosphorus rises to levels three or four times those present with adequate renal function. This is often but not always accompanied by a decrease in total and in ionizable calcium (15a-d). The latter change only rarely produces tetany and then only when alkali has been given. In some patients the drop in calcium does not occur and in these it is reasonable to suspect that secondary hyperparathyroidism has developed (16a-g). The sodium, chloride, and potassium levels are often well maintained despite restricted renal excretory ability until the terminal stages. At this point the concentrations of the first two tend to be set lower, often in conjunction with edema as a consequence of the osmoreceptor and volume receptor changes discussed in chapter 19. Also, the level of the potassium tends to rise (see fig. 9-9). These interrelations are readily evident in many of the patients whose values are shown in figure 12-9; the common character of these changes, whatever may be the etiology or pathological diagnosis of the renal failure, is illustrated in table 12-II.



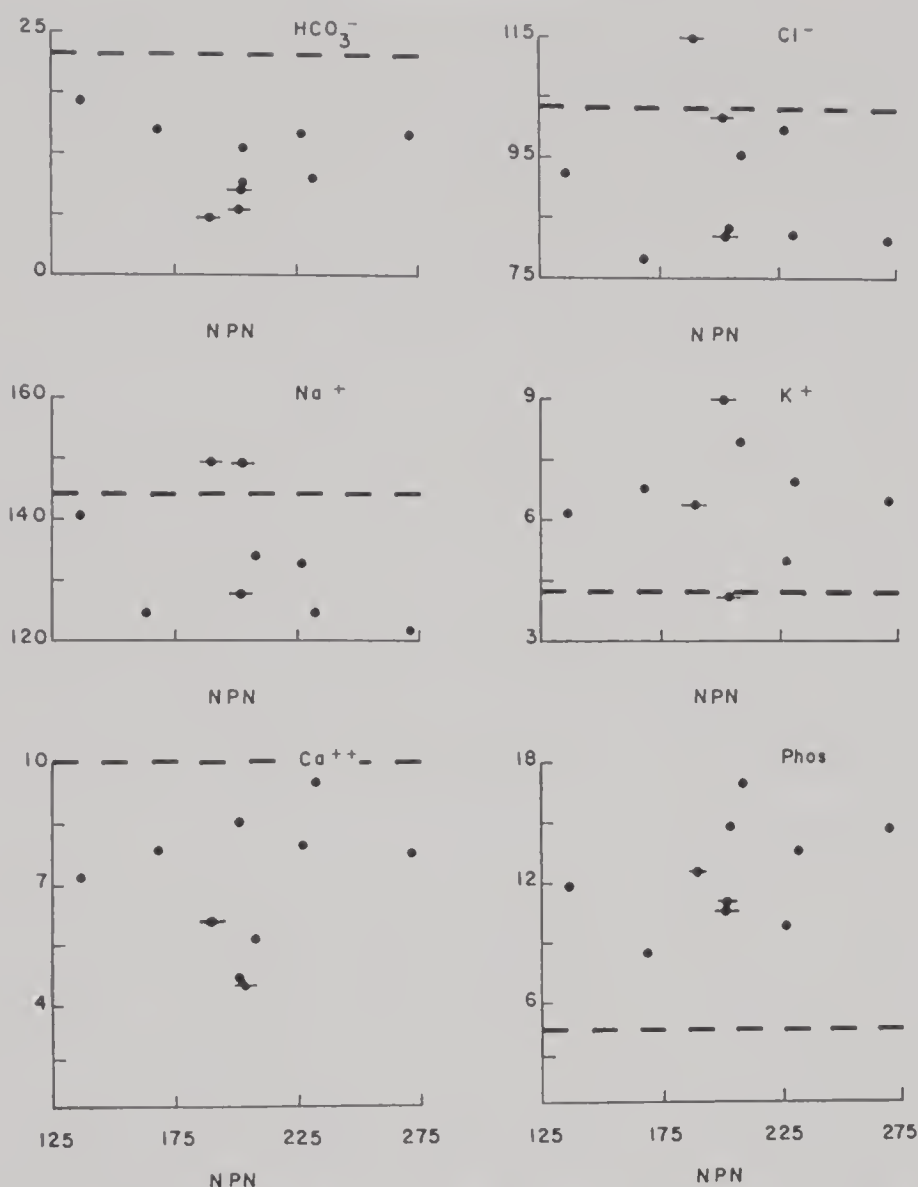


FIG. 12-9. SERUM ELECTROLYTES IN CHRONIC RENAL FAILURE

It is clear that far-advanced renal failure of some duration produces electrolyte changes quite comparable to those seen with acute renal disease in fig. 12-4. (From Mateer and Danowski, unpublished data.)

In a few rare cases sodium-wasting or potassium-wasting nephritis appears (17a-g, 18a, b), and recently a "water-losing" nephritis simulating diabetes insipidus has been described in a case of myelomatosis (18c); the latter does not appear in the usual types of chronic renal failure.

### C. Therapy

Therapy of some of these derangements is feasible. Thus deficits of bicarbonate, calcium, sodium and chloride can be replaced. To prevent tetany calcium salts should always precede use of alkalis such as bicarbonate. Maintenance of salt balance over long periods of time requires careful assessment of each individual patient. Some patients with chronic renal

TABLE 12-II.

ABNORMAL PATTERNS OF SERUM ELECTROLYTE CONCENTRATION IN PATIENTS WITH AZOTEMIA AND RENAL FAILURE DUE TO VARIOUS DISEASES								
RENAL DISEASE*	DAILY URINE VOL.  (ml.)	SERUM CONCENTRATION						
		CO <sub>2</sub>	Cl	Na	Na- (CO <sub>2</sub> +Cl)	K	PO <sub>4</sub>	Ca
					(mEq./l.)		(mg%)	(mg%)
Acute Glom. <sup>+++</sup>	50	17	86	124	22	6.4	12.1	8.7
Chr. Glom. <sup>o</sup>	1360	19	84	121	18		7.4	11.8
Pyeloneph. <sup>o</sup>	300	9	104	134	21	3.8	2.3	8.9
Nephroscl. <sup>++</sup>	0	5	95	128	28	6.7	13.6	-
Nephroscl. <sup>o</sup>	600+	18	100	141	23	4.6	6.5	7.8
Lower Neph. <sup>+++</sup>	75	13	77	116	26	7.2	8.7	6.2
Intracap. <sup>++</sup> Glom. Scl.	740	14	94	135	28	5.8	13.6	-
Normal subject average		27	103	138	4-11	3.5-5.3	4.0	10.0

\* o to +++ refers to degree of edema

failure require daily doses of sodium salts to prevent salt depletion, increased azotemia, and severe metabolic acidosis (fig. 12-10). Others do not, and the administration of sodium bicarbonate or sodium chloride leads to congestive heart failure, edema, and hypertension. The patient must be "titrated" between these alternate hazards. Prolonged ingestion of sodium lactate by these patients, recently suggested (19a), only leads to these latter complications, in our experience (fig. 12-11). Excesses of phosphorus and potassium can be removed in part by aluminum hydroxide gels and by exchange resins respectively (19b-d, 9v). None of these methods decreases the high levels of non-protein nitrogen. This manifestation of renal failure as well as any excesses or deficiencies of any of the other solutes save the macro molecules, can be corrected by vivo-dialysis by means of the artificial kidney as discussed in detail in chapter 25. This last procedure may prolong the survival of chronic renal failure beyond an episode that otherwise would have been a fatal exacerbation or acceleration of the disease.

Homologous kidney transplantation has been attempted in a few patients with severe renal failure, but uniformly without success. The most complete clinical and experimental study of this procedure is that of Hume, Merrill, Miller, and Thorn (19e); the reader is referred to their paper which contains a complete review of the literature. In four of their nine cases, the trans-

Patient: J. DiV, 50 d W, Chronic renal insufficiency with uremic acidosis.

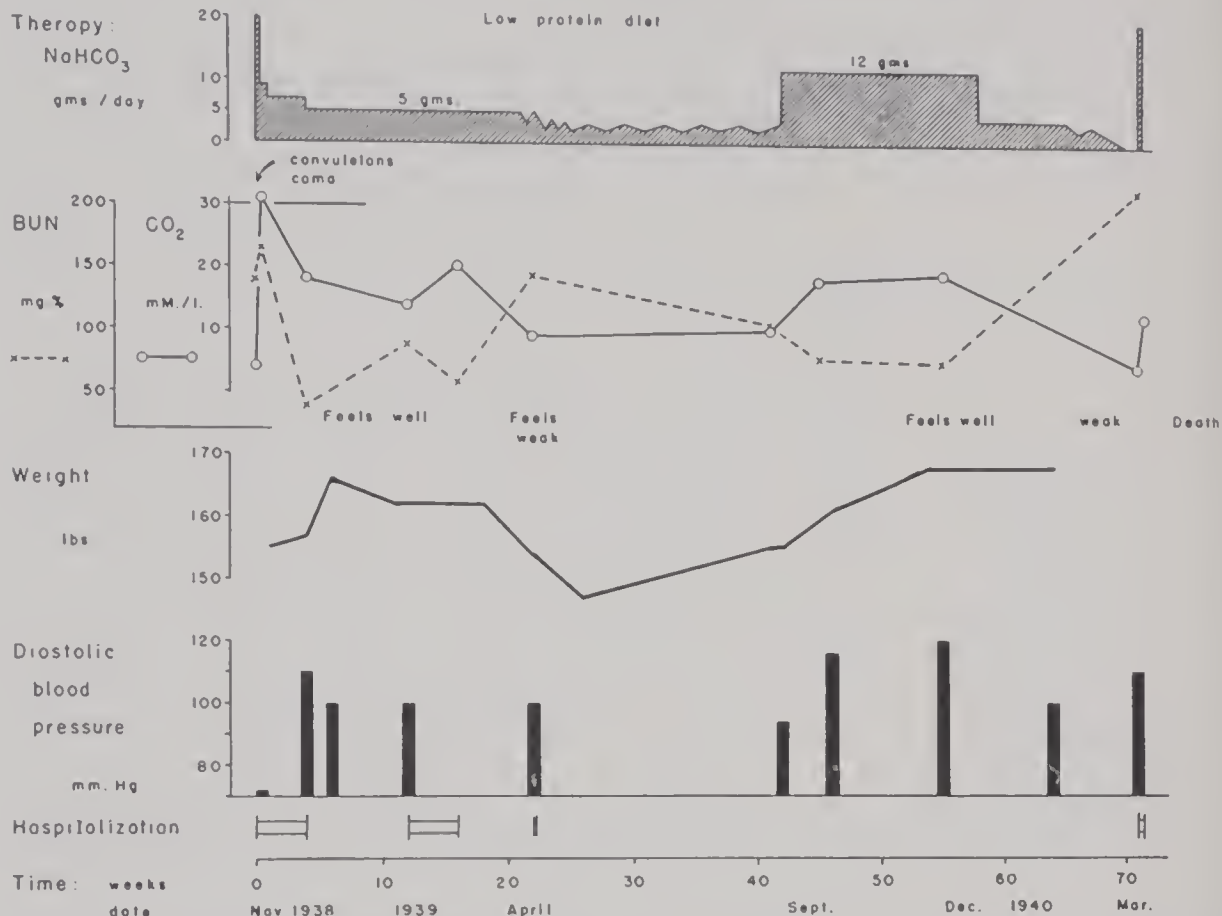


FIG. 12-10. PROLONGED SODIUM BICARBONATE THERAPY IN CHRONIC RENAL FAILURE

This patient was first seen in severe uremia with a marked metabolic acidosis, coma, and convulsions. Treatment with intravenous solutions of sodium bicarbonate and calcium restored the patient to an ambulatory state. Following discharge from the hospital, the patient was maintained as an outpatient for approximately  $1\frac{1}{2}$  years, on daily doses of sodium bicarbonate. Too little of the alkali permitted exacerbation of the acidosis, too much induced hypertension. (Unpublished study by Elkin-ton.)

planted kidneys excreted urine for periods of 37 to 180 days and developed function up to 25 per cent of normal; but in the end the host tissues rejected all the transplants. At present this procedure is not warranted in the treatment of irreversible renal insufficiency.

Some comment should be made concerning protein intake in the terminal phase of nephritis. Laboratory studies indicate that survival is decreased by high protein feedings to animals with diminished kidney parenchyma (20a-c). This evidence, together with the knowledge that protein foods contain potassium in significant amounts, can be taken to indicate the desirability of limiting the intake of this foodstuff. On the other hand, restriction of protein to zero will only accelerate breakdown of tissue protein. Hence a middle-of-the-road program is best, i.e., provision of enough protein, perhaps 25 grams each day (without potassium if accumula-



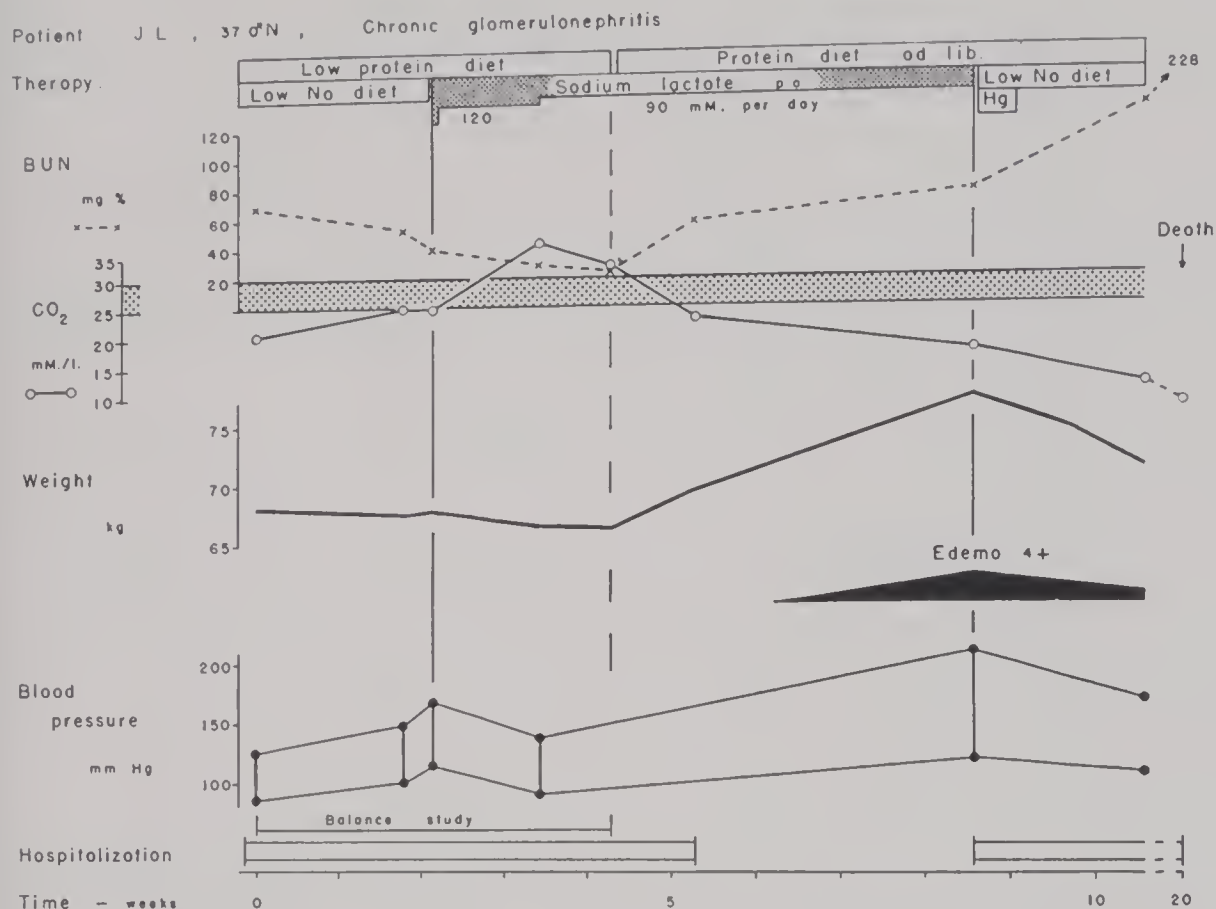


FIG. 12-11. THE RELATIVE EFFECTS OF LOW AND HIGH INTAKES OF PROTEIN AND SODIUM IN THE TREATMENT OF CHRONIC RENAL FAILURE

The azotemia and acidosis improved on the low protein diet before the start of the sodium lactate therapy, and regressed on an *ad libitum* protein intake while still receiving the sodium lactate. Although the patient came into equilibrium in respect to sodium balance during the early balance study, severe edema and hypertension developed while the high sodium intake was extended from the 5th to the 9th week of study. (Unpublished case study by Bluemle and Elkinton.)

tion of this ion is a hazard) to maintain balances of tissue nitrogen (9p, 20a-d). A diet deficient of protein will by itself produce tubular damage (20e).

## V. Syndromes of Specific Tubular Dysfunction

In recent years many disturbances in renal function have been described which primarily involve the renal tubule rather than the glomerulus or the nephron as a unit. These disturbances may be acquired or inherited and may involve one specific function or many functions of the tubule. Such tubular dysfunction leads to a variety of metabolic sequelae and clinical syndromes which are often confusing as to cause and effect. Furthermore, tubular damage may result in localized calcification in the kidney and in generalized changes in the calcification of the skeleton; primary diseases of calcium and phosphorus metabolism may cause renal damage. The

TABLE 12-III

RENAL RICKETS AND PRIMARY HYPERPARATHYROIDISM COMPARED WITH RENAL TUBULAR ACIDOSIS AND THE FANCONI SYNDROME*						
Diagnosis	Normal ** Subjects	Renal Rickets (Chr. gl.N.)	Hyperpara- thyroidism	Renal Tubular Acidosis with osteo- malacia	without osteomalacia	Fanconi syndrome
Patient Date		E.R.	S.S. Mar. Jun.	H.L.	A.T. 1950 1953	D.B. Feb. 1953
A. BLOOD AND SERUM						
BLOOD: urea-N.mg%	12 - 20	200	80	13	15	34\$
Arterial pH	7.36- 7.46	7.32	27		6.98	
SERUM: CO <sub>2</sub>	26 31	12	27	20	4	24 - 3.6
Cl	99 -106	75	92	93	120	112 -118
Na	136 -148	128	129	136	136	142 -146
Na- (CO <sub>2</sub> +Cl)	0 - 11	41	10	23	12	
K	3.5 - 5.5	6.1	4.2	4.6	2.5	3.1- 3.8
Alk.phosphatase B.U.	2 - 8.6		12.1	8.5	8.3	13.3- 22.0
Ca	9 - 11	7.6	16.4	8.9	12.0	9.8- 10.6
PO <sub>4</sub>	3.5 - 4.5	12.9	4.1 2.7	1.9	0.9	2.6- 3.2
B. RENAL FINDINGS						
Urine pH	< 6.0*			6.88	8.07	7.5
RENAL EXCRETION:						
HCO <sub>3</sub>	0*					
Ca <sup>++</sup> (low Ca diet)	<150		63	11	24†	
(NH <sub>4</sub> Cl diet)			300	23	350†	
Organic acids	27 - 50			80		
Amino acids	0			75		
Glucose	0			0		
				0		Incr. 0.8- 6.3

RENAL CLEARANCE:					
Cinulin	ml/min/1.73 M <sup>2</sup>	109	± 14	2.6	8.8
Ccreatinine	ml/min	<5*			56
CP0 <sub>4</sub> /C	creat.	0.03-	0.05*		14.4
T <sub>m</sub> PAH	mg/min/1.73 M <sup>2</sup>	77	± 11	0.2	0.26
					89†
					30
					55*
					127
					12.2
					0.11
					80

# Cases studied by the authors and their associates  
 \*\* Range within which approximately 95 per cent of healthy subjects fall.  
 See Chapter 4 for age, sex and other differences  
 § NPN  
 \* In an acidotic subject  
 † Determined in March 1950  
 ★ At plasma phosphate levels 3.0 mg%  
 ‡ mEq/gram creatinine/day (Unpublished studies J.R.E.)



differentiation of these abnormalities and their relation to specific renal tubular dysfunction, are discussed in this section.

#### A. "Renal Rickets" Differentiated

This term is best confined to those states of acute or chronic renal failure in which the rate of glomerular filtration is so low that the renal clearance of phosphate is less than the rate of intake and catabolic accumulation of phosphate. The consequence is an elevated phosphate in serum and extracellular fluid and a metabolic acidosis. Frequently, but not always, the serum calcium level is depressed; this has been attributed to increased calcium phosphate deposition secondary to the phosphate retention. In some cases this hypocalcemia disappears over time, a fact that led to the concept of secondary hyperparathyroidism in chronic renal failure. Hyperphosphatemia may also stimulate parathyroid activity. These factors of calcium and phosphorus metabolism in renal insufficiency have been clarified primarily by Albright and associates (21a, b) as well as by Talbot *et al.* (21c, d).

Renal rickets due to glomerular inadequacy is differentiated from the other states of predominantly tubular dysfunction by the *high serum phosphate concentration* and *severe azotemia*. Serum calcium levels may or may not be depressed, low  $\text{CO}_2$  and bicarbonate concentrations indicate the common metabolic acidosis of uremia (see tables 12-II and 12-III).

#### B. Tubular Dysfunction Due to Extrinsic Factors

1. **Acute tubular necrosis** resulting from nephrotoxic agents or renal anoxia has already been discussed in detail and will not be further elaborated. In the early stages, glomerular as well as tubular function is severely depressed (fig. 12-1) and the biochemical pattern of renal rickets as just described, ensues. In the polyuric phase of the disease when the progressive resumption of glomerular filtration precedes that of tubular function, inadequate reabsorption of various constituents of the filtrate may lead to multiple electrolyte deficits and dehydration.

2. **Primary hyperparathyroidism** not infrequently results in nephrolithiasis and in tubular damage with or without nephrocalcinosis (21b, e, f). Whether or not it is true that the hormone or hormones of the parathyroid gland act by mobilizing calcium from bone, as well as inhibiting reabsorption of phosphate, it is quite evident that excessive amounts of calcium and phosphate are excreted in the urine. The clinical symptoms are nausea, vomiting, and weakness, the x-ray findings are those of generalized or localized skeletal decalcification (osteitis fibrosa cystica). The biochemical signs are hypercalcemia (in relation to plasma protein level) and hypophosphatemia, and an excessive excretion of calcium in the urine ( $>150$

Patient: S.S., 71♀W, Primary hyperparathyroidism with renal insufficiency, nephrosclerosis

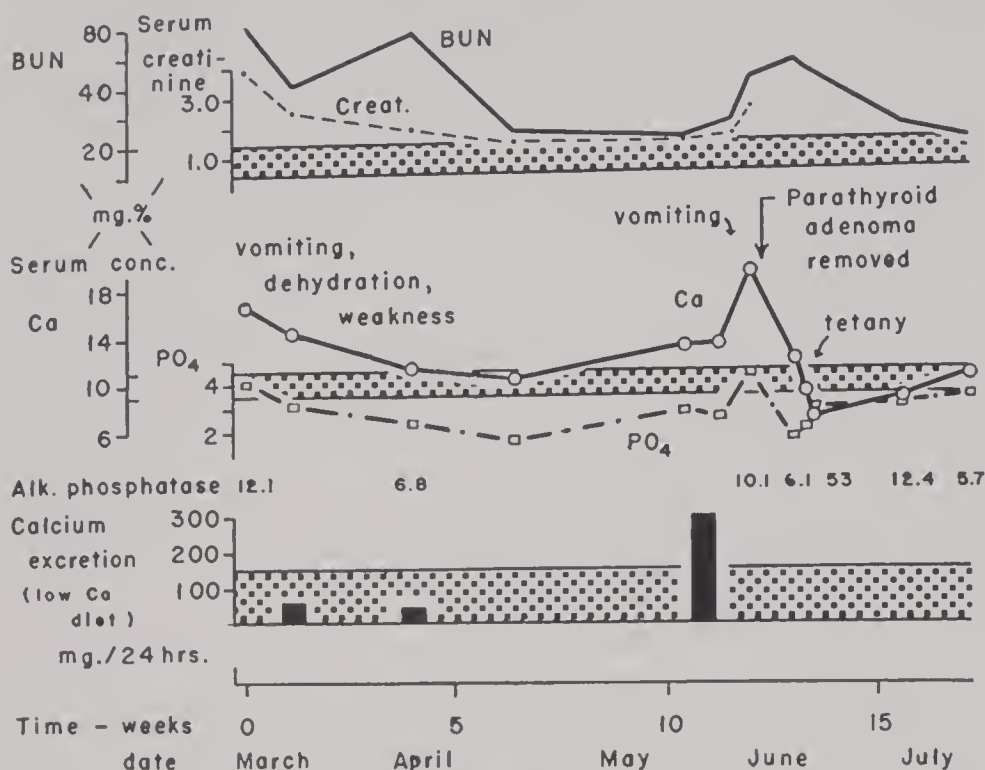


FIG. 12-12. PRIMARY HYPERPARATHYROIDISM COMPLICATED BY CONCOMITANT RENAL INSUFFICIENCY

Early in the hospital course the failure of renal function, due at least in part to dehydration and nephrosclerosis, resulted in *relative* hyperphosphatemia and in a low rate of excretion of calcium on a low calcium diet. Later, when renal function was improved, the calcium excretion rate became elevated and, with the hypophosphatemia and hypercalcemia, supported the diagnosis of hyperparathyroidism. (Unpublished study by Elkinton and associates.)

mg. per day) on a low calcium diet (table 12-III). Associated glomerular insufficiency due to circulatory failure, nephrosclerosis, pyelonephritis, etc. will obscure the diagnosis. This is illustrated by the case shown in figure 12-12, where the renal insufficiency resulted in *relative* hyperphosphatemia and in a low rate of excretion of calcium on a low calcium diet.

**3. Vitamin D intoxication**, producing hypercalcemia and sometimes nephrocalcinosis, may result in renal damage and renal failure (14d, 21g, h). Such damage involves the glomeruli and tubules; azotemia and fixed low urinary specific gravity result.

**4. Alkali ingestion and metabolic alkalosis** have frequently been found in association with renal insufficiency (22a-e). Burnett *et al.* (22f) have stated the salient features of this syndrome in the title of their paper, "Hypercalcemia without hypercalcuria or hypophosphatemia, calcinosis, and renal insufficiency; a syndrome following prolonged intake of milk and alkali." Vomiting due to pyloric obstruction is usually a factor in the pro-

duction of the metabolic alkalosis. Studies of renal dynamics (22g) show depression of both glomerular and tubular function, which persists for many months. Cooke and Kleeman (22h) have reported the cases of two siblings with nephrocalcinosis and metabolic acidosis who had congenital pyloric stenosis; it is suggested that the associated alkalosis and potassium deficit might have been responsible for the renal damage.

**5. Potassium deficiency and renal tubular damage** are frequently associated, but the sequence of cause and effect is not always clear. Potassium loss occurs in the polyuric phase of acute renal failure, as has been described earlier in this chapter; potassium wasting is one consequence of some of the intrinsic tubular defects discussed below. On the other hand, potassium deficiency *per se* appears to be responsible for depression of tubular function (22i). The situation is further complicated by the interrelationship of certain types of potassium deficiency and metabolic alkalosis (see chapter 11).

### *C. Intrinsic Defects of the Renal Tubules*

The manifestations of renal tubular malfunction are usually multiple, a fact not surprising in view of the multitudinous reabsorptive and secretory functions of the tubular cells. This is especially true when the abnormalities are acquired as the result of some widespread disease of the kidney, such as glomerulo- or pyelonephritis. On the other hand, failure of a single biochemical transport system, such as that required for the reabsorption of a specific amino-acid, may be genetically determined. In either case the tubular abnormality can be said to be "intrinsic" in origin as compared to those just described.

**1. Renal tubular acidosis** is a more convenient name for the syndrome first described by Butler, Wilson, and Farber (23a) and elucidated in detail by Albright and associates (23b, c, 21b); the name proposed by the latter was "renal acidosis resulting from tubular insufficiency without glomerular insufficiency." This condition may occur with or without clinical and x-ray evidence of *osteomalacia*, the "pseudofractures" of Milkman (23d). In the absence of such x-ray evidence, the constant finding of *hypophosphatemia* with serum levels of calcium near or within the normal range indicates, according to Albright, "chemical osteomalacia." In addition, these patients exhibit, either spontaneously or on an acid diet, a *metabolic acidosis* with lowered values for bicarbonate and buffer base concentration and for arterial pH (table 12-III). This acidosis is distinguished from that of uremia by the *absence of azotemia*. The low serum bicarbonate may be found with a *hyperchloremia* or with an increased concentration of "undetermined anion" (organic acids?). Deficits of fixed cations, calcium,



potassium, and sodium, take place in variable combination and to variable degrees. Clinical symptoms of deficits of these several cations may appear. Excessive excretion of calcium sometimes leads to nephrocalcinosis. The syndrome has now been studied by a series of investigators (23e-u), and it appears that there is considerable overlap with the Fanconi syndrome (described below).

The etiology of this condition may be genetic since familial occurrence has been reported (23q), or may possibly be due to such non-specific factors as recurring pyelonephritis (21b, 23c). Although some degree of impaired glomerular filtration is often present, the disturbances in renal function are primarily tubular, and standard indices of tubular function, such as PAH Tm and extraction, are depressed (23o, u-w) (table 12-III). The principal tubular defect is impairment of the mechanism for reabsorption of bicarbonate and the acidification of the urine. Albright *et al.* postulated this to be a distal tubular defect in the secretion of hydrogen and ammonium ions. Latner and Burnard (23n), studying infants with hyperchloremic acidosis, found evidence for a defect in the proximal tubular reabsorption of bicarbonate. With the recent evidence for an ion exchange in both segments of the tubule (see chapter 11), it is not clear that the reabsorption of bicarbonate and the secretion of hydrogen can be separated. In any case, the abnormal excretion of bicarbonate leads to failure of conservation of fixed cations, potassium, sodium, and calcium, as well as to a systemic acidosis. The inability of the kidney to acidify the urine and to conserve fixed cations may be demonstrated, as Albright *et al.* (21b, 23c) showed, by the administration of ammonium chloride. Such a test in one of our patients is illustrated in figure 12-13.

These patients exhibit an abnormally high clearance and excretion rate of phosphate with a resultant hypophosphatemia. Albright *et al.* suggested that this was due to secondary stimulation of the parathyroids by the hypocalcemia consequent to the renal wasting of calcium; evidence for an intrinsic tubular defect in phosphate reabsorption is not clear (23p). Other defects in tubular transport resulting in glycosuria, amino-aciduria, and organic aciduria (23x) have been found in these patients, findings that support the view that renal tubular acidosis and the Fanconi syndrome are not two clearly differentiated clinical diseases (23p, t, y, z).

Treatment of renal tubular acidosis consists primarily of immediate replacement of deficits of potassium and sodium and subsequent prevention of cation losses over prolonged periods of time; this latter regimen consists in the daily administration of enough extra cation in the form of sodium bicarbonate (4 to 6 grams) or sodium citrate to replace abnormal losses of fixed cation in the urine. In patients with osteomalacia sodium

A.T., 38 ♀ W.

 $\text{NH}_4\text{Cl}$  test

March 17–28, 1950

Therapy

Serum conc.

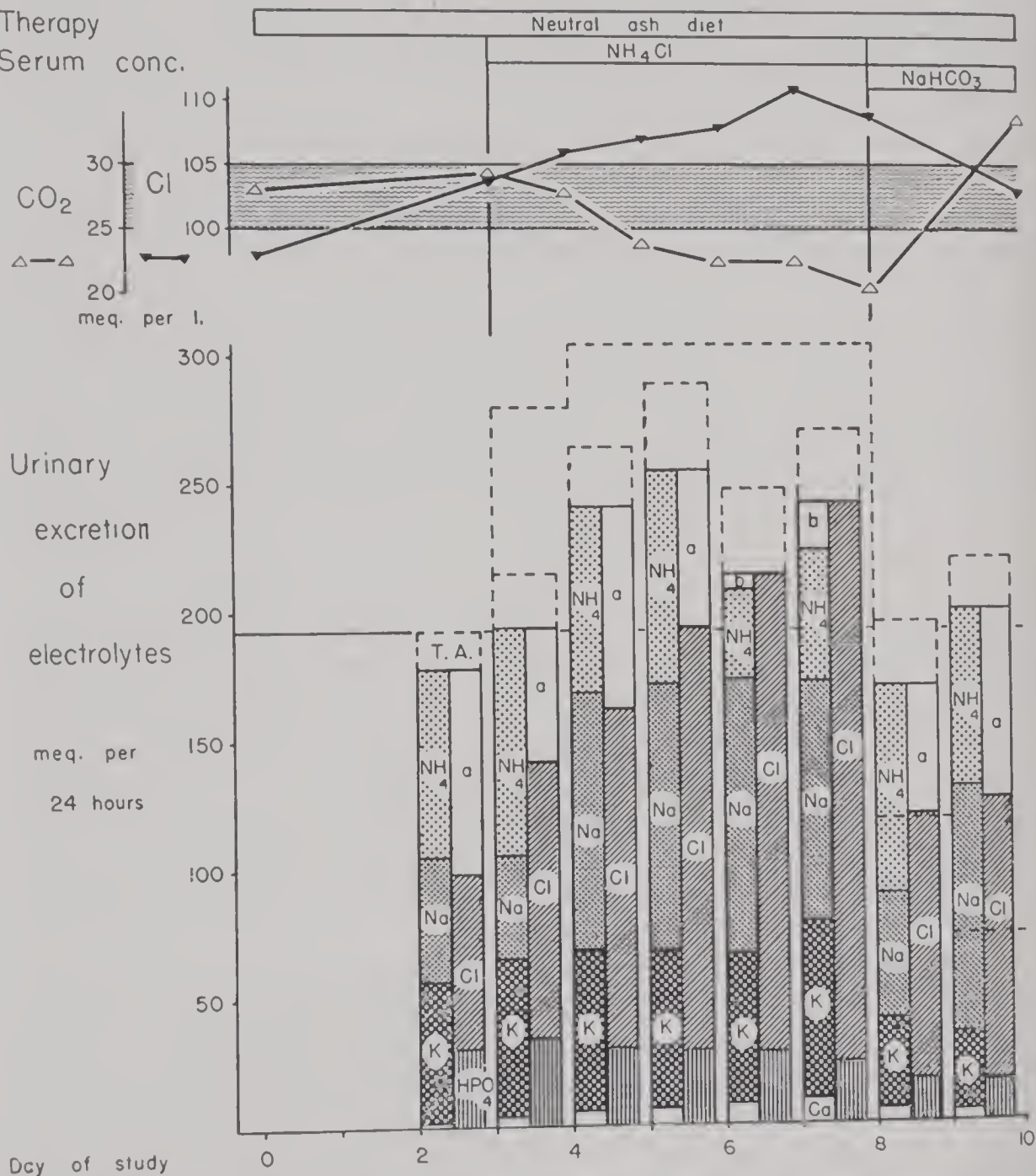


FIG. 12-13. RENAL TUBULAR ACIDOSIS: DEMONSTRATION OF TUBULAR INABILITY TO SECRETE HYDROGEN AND AMMONIA BY ADMINISTRATION OF AMMONIUM CHLORIDE AS AN ACID LOAD

The broken line indicates the 112 mEq. of chloride ion added per day to the renal excretory load, above the control level. In the normal subject the increased production of ammonium ion and titratable acidity (T.A.) permits the excretion of the excess anion,  $\text{Cl}^-$  (as did this patient after recovery, fig. 10-7). Here, the failure of these mechanisms resulted in increased excretion of fixed cations, sodium, potassium, and calcium, and in a metabolic acidosis. (From Elkinton *et al.* (23u).)

citrate is preferable and may be given in the form (50 to 100 ml. per day) of Shohl's solution (21b), which has the following composition:

Sodium citrate.....	98 gm.
Citric acid.....	140 "
Water.....	1000 ml.

In patients without overt osteomalacia it is simpler to use sodium bicarbonate. If edema results from the sodium with the bicarbonate or citrate, the potassium salt may be substituted in part. The alkali therapy is preventive and does not repair the osteomalacia. This requires a high calcium diet and large doses of vitamin D.

**2. The syndrome** first described by **Fanconi** and deToni (24a-c) is characterized by aminoaciduria, glycosuria, hyperphosphaturia with hypophosphatemia, and osteomalacia (table 12-III). Fanconi attributed these findings to failure of normal reabsorptive processes in the renal tubule. This has been confirmed subsequently by a series of investigators who have added much to our knowledge of these abnormalities (23g, p, s, t, w, y, z, 24d-l). Originally this syndrome was thought to be a disease of infancy or childhood; however, Stowers and Dent, Milne, Stanbury and Thomson, and others have now described it in adult patients in some of whom the signs of renal tubular acidosis were also found (24h, 23p, t, w). It is apparent, therefore, that these two syndromes are not two distinct and separate entities but rather are overlapping combinations of multiple tubular abnormalities. The etiology also is probably multiple in nature and in some cases appears to be hereditary (23z, 24g, h); Stowers and Dent (24h) found evidence in their case of transmission of the tubular defect by a Mendelian dominant gene. Genetic considerations of these two syndromes, and of cystinuria (24m) and Wilson's disease with aminoaciduria (24n, o) are concisely reviewed by Jackson and Linder (23z); a modification of the latters' classification of tubular defects is given below.

Treatment of the Fanconi syndrome is similar to that outlined above for renal tubular acidosis; cation deficits must be replaced and prevented, osteomalacia requires vigorous treatment with vitamin D and high calcium diets. Methyl testosterone has been reported to be of benefit (23y).

**3. Syndromes of renal potassium wastage** are being clarified. Hypokalemia has been reported in various types of renal disease: chronic glomerulonephritis (25a-e), nephrosclerosis (8k, 25f, g, m), polycystic disease (25c, d), and renal insufficiency of uncertain or unspecified origin (8k, 25c, h). Intracellular potassium deficiency and hypokalemia are frequently present in cases of renal tubular acidosis and the Fanconi syndrome, as described above. In addition a few rare cases have been reported of potassium deficiency associated with specific tubular wastage of the ion (18a, b,



25i, j). In the case studied by Squires, Huth, and Elkinton (18b) the hypokalemia was associated with a high rate of tubular secretion of the ion and an inability to respond normally to the carbonic anhydrase inhibitor, 6063 or "Diamox." These findings suggested a specific deficiency of the enzyme carbonic anhydrase in the renal tubule with a low rate of secretion of hydrogen and a reciprocally high rate of secretion of potassium. After reviewing the literature, Squires *et al.* suggest three categories of renal potassium wastage: 1) late non-specific potassium wastage in chronic renal disease, 2) potassium wastage due to defective tubular mechanism of acidification and bicarbonate reabsorption, as found in renal tubular acidosis and the Fanconi syndrome, and 3) specific tubular secretory wastage, possibly related to deficiency of the enzyme carbonic anhydrase. To these three categories a fourth must be added, namely, potassium wastage due to an excessive secretion of an adrenocortical steroid similar to, or identical with, aldosterone. Such a steroid was found in the urine of the cases of Evans and Milne (25j, k), of Squires *et al.* (18b), and of Conn (25l). In Conn's case an adrenocortical tumor was removed with correction of the potassium abnormality.

**4. Renal diabetes insipidus** indicates a defect in the tubular reabsorption of water in the presence of an intact supra-optico-hypophyseal system for the elaboration of antidiuretic hormone. Polyuria leading to dehydration occurs in the diuretic or healing phase of acute renal failure due to tubular necrosis (1e, 10i) and rarely in some cases of severe chronic renal disease with low glomerular filtration and tubular damage (18c). In addition, certain cases, often with one or more of the Fanconi stigmata of glycosuria aminoaciduria, or organic aciduria, have been found to exhibit defective tubular reabsorption of water which is unresponsive to endogenous or exogenous antidiuretic substances (23z, 24d, g, j, 26a-f). In some of these cases this abnormality appeared to be an inherited sex-linked recessive characteristic (23z, 26d, e); in none of the cases was the specific gravity of the urine as low as in the classical diabetes insipidus of pituitary origin.

**5. Idiopathic hypercalcuria** appears to be a specific defect in the tubular reabsorption of calcium (27a, 21b). It is associated with nephrolithiasis; "chemical" osteomalacia is more common than "overt" osteomalacia. Acidosis is not present and alkali therapy is unavailing; the advantage of calcium and vitamin D therapy for the osteomalacia must be weighed against the possible effect of increased calcium excretion on the renal stones.

**6. Vitamin D resistant rickets** is the result of hyperphosphaturia due to defective tubular reabsorption of phosphate, without the other signs of the Fanconi syndrome (27b-d). Since Stowers and Dent (24h) found a deficiency of the enzyme phosphatase in the proximal tubules of one of

their cases with the Fanconi syndrome, it is possible that such a mechanism of deficient phosphorylation plays a part in the failure of phosphate reabsorption.

**7. Pseudohypoparathyroidism** is a rare condition with hypocalcemia and hyperphosphatemia which are apparently the result of an abnormally high rate of reabsorption of phosphate (28a-d), hence is the opposite of vitamin D resistant rickets.

**8. Aminoaciduria** has been found in many of the above syndromes and has been studied most extensively by Dent and his co-workers (24h, i, m) using the technic of paper chromatography. In their own cases and in the Fanconi patient of Milne, Stanbury, and Thomson (23p) the following amino acids were identified in excessive amounts in the urine: phenylalanine, aspartic acid, leucine, valine, tyrosine, histidine, citrulline, arginine, lysine, glutamine, alanine, threonine, glycine, serine, hydroproline, aminobutyric acid, and proline. Cystine was reported in the latter case but Dent and associates are of the belief that there is no overlap between the Fanconi syndrome and congenital cystinuria and cystinosis (24h, m). Beumer and Wepler (29a) believe the two diseases are related.

Aminoaciduria has been reported in cases without the other Fanconi findings (29b) and it is an important feature of the syndrome of hepatolenticular degeneration or Wilson's disease (24n). It has been reported in cases of lead poisoning (29c, d). Lathem, Baker, and Bradley (29e) found most of the above-listed aminoacids in abnormal amounts in the urine of a Fanconi case; but the urinary pattern of amino-acids in 15 patients with severe acute and chronic renal disease did not differ from that of normal subjects. This suggests that the aminoaciduria of the Fanconi syndrome is related to some factor other than that of general tubular damage.

**9. A summary** of the clinical syndromes and factors involved in *intrinsic renal tubular defects* has been made by Jackson and Linder (23z), and follows in a slightly modified form.

*i. Unifactoral conditions:*

A. Deficient tubular reabsorption of :

1. Water → Renal diabetes insipidus.
2. Glucose → Renal glycosuria.
3. Phosphate → Vitamin D resistant rickets.
4. Calcium → Idiopathic hypercalcuria.
5. Bicarbonate → Hyperchloremic renal tubular acidosis.
6. Organic acids → Organic aciduria.
7. Aminoacids → Renal aminoaciduria, Wilson's disease.
8. Cystine → Simple congenital cystinuria.

## B. Excessive tubular secretion of:

1. Potassium  $\rightarrow$  Specific renal potassium wastage.

## C. Excessive tubular reabsorption of:

1. Phosphate  $\rightarrow$  Pseudohypoparathyroidism.

*ii. Multifactorial conditions:*

## A. Deficient tubular reabsorption of:

1. Glucose + phosphate  $\rightarrow$  glycosuric rickets.
2. Glucose + phosphate + aminoacids  $\rightarrow$  classical Fanconi syndrome.
3. Phosphate + bicarbonate + organic acid  $\rightarrow$  hyper- or hypochloremic renal tubular acidosis.

Associated renal wastage of:

- a. Calcium  $\rightarrow$  osteomalacia.
- b. Potassium  $\rightarrow$  hypokalemic syndrome.
- c. Sodium  $\rightarrow$  salt depletion.

4. Numbers 2 and 3 may be combined.

**SUMMARY:** Acute renal failure arises most often from reversible tubular damage due to transfusion reaction, crush injury, anoxia from shock and inadequate renal blood flow, or nephrotoxic agents such as mercury, carbon tetrachloride, and sulfonamides.

Diagnosis is based on the occurrence of anuria, azotemia as indicated by rising BUN or NPN, an increase in serum undetermined anions ( $\text{Na} - [\text{CO}_2 + \text{Cl}]$ ), a rise in serum phosphorus and a drop in calcium, falling serum concentration of  $\text{CO}_2$  with ultimate hyperventilation, and increases in serum K with ECG evidence of hyperkalemia, accompanied by progressive mental confusion, twitching and tetany.

Fluid disturbances which characterize acute renal failure include oliguria or anuria, progressive metabolic acidosis as a consequence of the retention of phosphates, sulfates, organic acids, and peripheral and pulmonary edema. The edema is particularly apt to appear if fluids are forced beyond extrarenal output of 1 liter or more per day. In the polyuric or recovery phase dehydration and sodium and potassium depletion may occur unless fluid loss is replaced.

Therapy, if anuria is due to nephrotoxic chemical, consists of an immediate infusion of 5 per cent glucose (1 liter) and 0.9 per cent NaCl (1 liter). Thereafter, and in other etiologies, the following program is followed: restrict total fluid intake to urine volume plus estimated exogenous need (about 600 ml. per day, higher if febrile); hypertonic sodium lactate (molar) or sodium bicarbonate (7.5 per cent) 1 to 4 40-50 ml. ampules plus equal or more volumes of 10 per cent glucose solution I.V. daily if serum



CO<sub>2</sub> content is less than 15–18 mM./l. and/or serum Na less than 129 mEq./l., provided that edema and/or hypertension is not excessive. Chloride solutions are contraindicated because of acidosis. Calories are to be supplied by means of a high carbohydrate, high fat diet if tolerated or glucose in peanut or cocoanut oil via polyvinyl tube in stomach. No meats or vegetables are to be given because of the potassium content. If ECG shows evidence of hyperkalemia or serum K concentration becomes greater than 6.0 mEq./l. give 1 to 3 high enemas per day of cation exchange resin in hydrogen or ammonium cycle (25 to 40 grams suspended in 250 to 400 ml. tap water), or use artificial kidney or peritoneal lavage if apparatus and experienced operators are available. Calcium gluconate, 1–3 grams I.V., is to be given daily whenever alkali is given. In the polyuric phase (after 3–21 days oliguria) it is advisable to expect continued toxic signs and rising azotemia for 2–4 days and to replace the total fluid loss (renal and extrarenal) with  $\frac{2}{3}$  to equal volumes of fluid p.o. and/or I.V., including sodium chloride and potassium as needed.

The same principles apply in the therapy of chronic renal failure. In entities with specific renal tubular dysfunctions treatment is adjusted to accord with the net disturbance in body fluids.

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## Chapter 13

### CONGESTIVE HEART FAILURE: A NEW STEADY STATE

Congestive heart failure, as its name implies, involves changes in the volume, distribution, and composition of body fluids.

Use of the balance procedures, tissue analyses and the volume of distribution or dilution technics described in chapters 3 and 4 has permitted quantitation of the degrees of body fluid changes in congestive heart failure. Such studies have indicated that excesses of sodium may be present within as well as outside of cells, that both extracellular and cellular volumes of water may be increased, that cell potassium may be diminished in amount and that the osmotic activity of cell base may be increased (1a-f). Concentrations of extracellular sodium are usually maintained within the range of normal in untreated patients despite the increases in the total amounts of this ion and in the total volume of body water (1g, h). In attempts to identify the physiologic changes responsible for these alterations in the volume, composition and distribution of body fluids, "backward failure" and "forward failure" theories have been advanced. These views are mechanical and, as a moment's reflection will indicate, are *in themselves* inadequate explanations of the factors which produce the body fluid changes. The chief objection to both views is that they do not explain why increments of salt and water are not continually added at such rates as to produce rapid expansions incompatible with survival. The fact that such patients do survive for prolonged periods suggests that the undue retention of salt and water is a limited process in congestive failure, and that the actual disorder involves disruption or a resetting of various regulators of volume, composition, and distribution of body water and solutes.

Evidence has been accumulating which points to the existence of such regulatory mechanisms. The presence in the hypothalamus of osmoreceptors which are sensitive to changes in extracellular osmolar concentration has



been indicated by the work of Verney, and evidence for receptors sensitive to changes in volume at some unidentified site has been obtained by other investigators (1i, j); these observations have been discussed in chapters 1 and 5. The studies of Leaf *et al.* and Weston *et al.* point to the establishment of new equilibria in body fluid volumes and composition by means of anti-diuretic substances (1k, l). However the relative constancy of the body weight and of the serum or plasma concentrations, as discussed in chapters 1 and 4, by themselves are evidence of the existence of such regulatory mechanisms. Indeed it is highly probable that a host of servo- or feed-back mechanisms maintain the volumes of plasma, interstitial fluid, cell water and the distributions of solutes therein within the narrow limits characteristic of health. In congestive heart failure new equilibria or new steady states are set up (1m). This is a far more acceptable explanation of the phenomena of congestive heart failure since it incorporates the essential components of forward and backward failure and at the same time offers a dynamic interpretation of how survival and activity are possible for prolonged periods. Although the older concepts will be reviewed in detail in this chapter with considerable emphasis upon contributing factors and mechanisms, these factors are only individual links in the chain of events leading from myocardial disease to the establishment of a new steady state.<sup>1</sup>

## I. The Role of the Heart in Fluid Retention: Older and Newer Views

For many years it has been held that congestive heart failure was a manifestation of an inability of the myocardium to pump the blood returned to it (1n). This was thought to lead to a backing up of blood with subsequent venous distension and enlargement of the liver. The increase in venous hydrostatic pressure which was readily demonstrable in such patients was held responsible for the edema and effusions which appeared. This view, frequently referred to as "backward failure," is of questionable validity since it is self-contradictory: it simultaneously assumes that a failing heart which cannot adequately perform its pumping function is more successful than usual in moving blood into certain segments of the circulation. The chief support for this objection has come from laboratory work: Starr, and others, have shown that it is impossible to simulate the manifestations of right-sided congestive heart failure simply by interfering with the pumping action or the efficiency of either mechanical or animal hearts (2a, b). Hence some other explanation had to be advanced. The formulation of an alternative and, to many but not to all workers, a more acceptable concept

<sup>1</sup> Strictly speaking, if the edema is increasing or decreasing, the body fluids are in a *transient state*. When the edema is being maintained relatively unchanged, however, it is proper to speak of a new *steady state*.

has been based on the accumulation of data by Stead, Warren and others on the output of blood by the heart, on the flow of blood through the kidney, on the factors which determine urine composition, and on the volume of the circulating blood and plasma. Though the results of some of these measurements represent approximations rather than precise values, they are of sufficient degrees of accuracy to provide an experimental basis for this newer alternative view of congestive heart failure referred to as "forward failure." In this concept the congestive phenomena are related to impaired renal excretion of sodium and water as a consequence of changes in cardiac output and renal function with resultant expansion of body fluids, if intake is maintained above the renal excretory limits. Detailed attention should be given to the intervening links of this chain, since it will permit the presentation of alternative views, point to areas of incomplete information, and lay a rational basis for current therapy of congestive heart failure.

## II. The Concept of Forward Failure

### A. Cardiac Output

In forward failure, the cardiac output of blood is decreased in absolute or in relative terms as a consequence of myocardial inadequacy. This is readily demonstrable in many but not all patients with congestive heart failure using the technic of cardiac catheterization (3a, b). Some overlap is present between groups of healthy subjects and patients with congestive failure. With increased physical activity this overlap disappears. A more definitive separation of these two categories of subjects under comparable degrees of activity is obtained if the oxygen content of "mixed venous blood," i.e., blood returning from all parts of the body, is measured in samples obtained by catheterization of the right atrium or ventricle. Such measurements show that in congestive failure the mean venous oxygen content is lowered (4). Evidence of anoxemia has led to some of the more comprehensive definitions of congestive heart failure: the condition in which "the heart is unable to maintain an efficient circulation when called upon to meet the efforts necessary to the daily life of the individual" (5a, b). This concept assumes of course that the supply of oxygen, and its transport through alveoli and via blood cells, is otherwise adequate. Such a view resolves some of the dilemma encountered in patients with beri-beri heart disease, arteriovenous shunts, anemia, or thyrotoxicosis in whom symptoms and signs of congestive failure are present despite an increased cardiac output which is still not sufficient to meet the tissue oxygen needs. However, it by no means disposes of the entire dilemma as we shall see in discussing the renal excretion of sodium in congestive failure.



### *B. The Role of the Kidney in Forward Failure*

It has long been recognized that the excretion of administered sodium is decreased in congestive failure (6a, b, c). In the concept of forward failure the following mechanism has been suggested to explain this fact. Measurements of renal blood flow in congestive heart failure frequently show a decrease which is out of proportion to the drop in cardiac output (3a, 7a, b). This decrease in renal blood flow usually, though not always, results in a diminished rate of glomerular filtration, even though the fraction of plasma converted into filtrate may rise in compensatory fashion to values considerably above the normal of 20 per cent (7a, b, 8a, b). Obviously the diminution in filtration rate inevitably lowers the amount of sodium presented to the tubules for reabsorption. Evidence has been advanced suggesting that the tubules reabsorb this electrolyte at a fixed maximal rate (9) and hence any decrease in filtered sodium automatically means that excreted sodium also diminishes. Hence, one school of thought attributes the decrease in sodium excretion to decreased glomerular filtration (7a, 8a, 9, 10a-c). This view is opposed by observers who have studied patients in whom sodium retention was present in the face of a normal glomerular filtration rate or in whom improvement occurred without a rise in filtration to normal, suggesting that excessive tubular reabsorption of this electrolyte was taking place (11a-d). There is no particular need for the clinical student of this subject to take one side or the other. It is probable that limitations in technique and variations among patients account for some of the differences. For our purpose it will suffice to accept the fact that in congestive heart failure sodium excretion is diminished and that glomerular filtration and tubular reabsorption both play a role. Whether this is mediated directly through the changes in renal hemodynamics as described above, or, as has been suggested by others, through rises in salt-absorbing steroids or other substances (12a-g), or via increases in intra-abdominal or renal vein pressures (13a-c), is unsettled. It is obvious however that a diminished glomerular filtration rate can hardly be advanced as an explanation for the sodium retention in the instances of high output failure; excessive tubular reabsorption is a more probable explanation. It would appear, therefore, that the abnormal conservation of sodium by the kidney in congestive heart failure is the result of a disturbance in the volume-regulating mechanism of the body and that multiple receptors and effector paths may be involved (c.f., figure 1-11 in chapter 1).

### *C. Starling's Laws and the Concept of Forward Failure*

Starling's studies indicate that within certain limits increases in venous pressure, or more precisely, increases in central or intracardiac pressure are



accompanied by an increase in the cardiac output (16). When the upper limit of this relationship is exceeded the net movement of blood by the heart falls. This will ultimately result in the relative or absolute expansion of plasma volume via the renal mechanisms described earlier. Clinically, the patient then shows venous distension, an elevation of the venous pressure, and a rise in the central pressure. Interference with the return of transudate to the circulation produces peripheral edema and accumulations of pleural, peritoneal, and pericardial fluids in accordance with the second of Starling's principles or "laws," i.e., that rising venous pressures increase capillary transudation (17).

Hence the concept of forward failure and Starling's "laws" are quite compatible.

### III. Changes in Body Fluids in Congestive Heart Failure

#### *A. Sodium and Water in Extracellular Fluid, Cells, and Plasma*

The result of an intake of sodium in excess of renal excretory ability is a retention of sodium. The osmoreceptor-antidiuresis apparatus which regulates solute-solvent relationships effects a retention of water. Since sodium is predominantly an extracellular ion, both the plasma and interstitial fluids expand in volume (1a-f). The extracellular concentration of sodium remains normal or slightly elevated (1c, h). Although transfers of sodium between extracellular and intracellular fluid have been reported to occur in both directions (1a, e), the osmotic activity of cell solutes appears to increase and the volume of cell water to rise (1a, c). Hence, the end result is an expansion of the fluid in all of the body compartments. (See figs. 3-12, 3-13, 3-14, 8-3 and tables 23-II to 23-VII).

The rise in plasma and blood volume is usually thought to be absolute, involving the greater and lesser circuits and the arterial and venous circulation to greater or lesser degrees (14a-d). However, some workers doubt that the plasma is actually expanded while others have suggested that the volume of plasma in relationship to the vascular tone, variations in the size of the vascular bed, or redistribution within vascular subdivisions, may be more important than the actual plasma or blood volume (15a-e).

#### *B. Chloride, Bicarbonate, and pH Changes in Congestive Heart Failure*

Studies in one of our laboratories (1g) indicate that patients with congestive heart failure frequently have high bicarbonate and low chloride concentrations in plasma. This presumably is related to the fact that such patients during diuresis tend to lose equivalent amounts of chloride and sodium whereas in the body sodium concentrations exceed those of chloride; a primary hypochloremic metabolic alkalosis then develops (1b, c). However in some of the patients the lowering of the chloride was attributable to

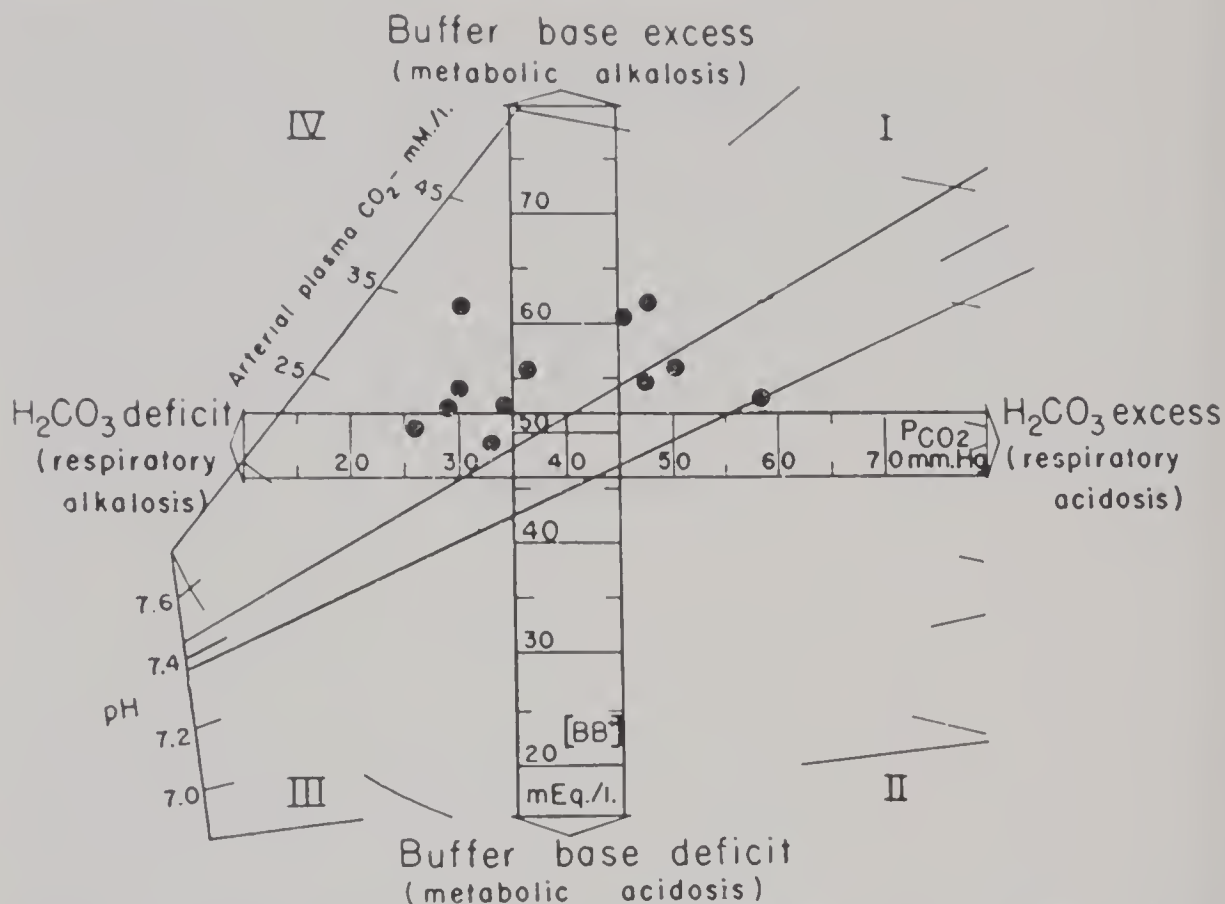


FIG. 13-1. DISTURBANCES IN ANION-CATION BALANCE AND pH IN CONGESTIVE HEART FAILURE

The two major variables of carbon dioxide pressure and buffer cation or base concentration, as determined in 12 edematous patients, are shown on the Singer grid (see fig. 11-12).

The high total  $\text{CO}_2$  content of venous serum in these patients was associated with an increase in buffer base concentration in most of the cases, indicating a component of metabolic alkalosis, presumably due to prior mercurial diuresis. In 4 of the 5 cases in which the  $\text{P}_{\text{CO}_2}$  was elevated (Quadrant I) the high pH indicated that this respiratory retention of  $\text{CO}_2$  was secondary to the primary metabolic alkalosis; a lesser primary  $\text{CO}_2$  retention due to inadequate pulmonary gas exchange cannot be ruled out. In the other cases with a respiratory  $\text{CO}_2$  deficit (Quadrant IV) this process must have been a primary one mixed with a primary metabolic excess of buffer base, since neither change is compensatory to the other; accordingly the pH change was more extreme.

It is apparent that the anion-cation balance and pH in this condition is the resultant of multiple processes which may affect both the metabolic and respiratory variables. (From Squires, Singer, Moffitt, and Elkinton (1g).)

primary  $\text{CO}_2$  retention as a consequence of cardiopulmonary disease with a secondary renal response (fig. 13-1). This is supported by the finding of elevated levels of  $\text{P}_{\text{CO}_2}$  in 4 of the 12 patients (1g), which pointed to the existence of a respiratory acidosis. In 6 other patients the  $\text{P}_{\text{CO}_2}$  was below normal indicating that a primary respiratory  $\text{CO}_2$  deficit was present in addition to the primary metabolic excess of buffer cation. In other words a variety of changes in both respiratory and metabolic factors determine

the precise anion-cation balance and pH in congestive heart failure. In this limited group of congestive heart failure cases there was no evidence that the undetermined anion fraction was greatly increased. Even though congestive failure alters renal function the clearance of undetermined anions appears to be well maintained even in those patients who develop moderate azotemia.

### *C. Serum and Cell Potassium in Congestive Heart Failure*

Deficits of potassium do occur in congestive failure. The inadequate intake of food in the face of a continued urinary loss of the electrolyte, and the tendency of diuretic agents such as mercury, carbonic anhydrase inhibitors, and of digitalis to accelerate urinary losses of potassium, all contribute to such deficits. The exchange of cell potassium for sodium in sodium retention has already been mentioned and may play a role in accelerating negative balances. Although, as in the case of sodium, deficits of potassium can coexist with high, low, or unchanged serum levels, the serum concentration is usually within the normal limits in those cases uncomplicated by renal insufficiency or vomiting (1g).

However, the absence of hypokalemia does not clearly exclude the possibility of intracellular deficits of this electrolyte. These have been demonstrated to be present in 3 of the 4 balance or isotope dilution studies cited earlier (1a-c, 1f). Also the simultaneous retention of potassium and the restoration of sodium levels to normal in congestive failure are suggestive evidence for cell deficits of potassium and excesses of sodium (15f, g). Hence the possibility of intracellular potassium deficit should be considered in any patient with congestive failure, although it is more apt to be present in those patients with a combination of hypochloremic alkalosis and hypokalemia.

## **IV. Hyponatremia without and with Sodium Depletion in Congestive Failure**

As indicated earlier the retention of sodium is accompanied by a retention of water. Hence in most instances of untreated congestive failure, serum sodium and chloride levels are not greatly different from those seen in healthy individuals (1h). However, in a certain number of patients with severe protracted congestive failure the serum sodium and chloride levels become lowered (1g). At first thought this might be attributed to salt depletion by virtue of the sodium restriction, mercurial diuretics, exchange resins, etc., which are inevitably employed in the treatment of such patients. That this frequently is not sodium depletion is evident from the observation that saline therapy most commonly does not result in improvement (19b). On the contrary it only serves to produce transient increases in the



concentrations of these electrolytes, at times associated with thirst, with an ultimate aggravation of the edema. The mechanism of this hypotonicity has not been elucidated. It appears to represent a resetting of the osmoreceptor-renal response mechanism at a new low level during this form of congestive failure with the result that it cannot decrease the expanded salt and water stores nor raise the concentrations to values present in health. It is possible that prolonged illness causes decreases in or losses of osmotically active constituents from cells and that this is in turn reflected in the generalized hypotonicity (1m, 18a, b). Though the origins of this development are uncertain its portent is definite: the development of hyponatremia of this type is an ominous sign that the patient will probably succumb (19a-c).

Another clinically important form of hyponatremia in congestive failure is that associated with true sodium depletion. Rigorous therapeutic measures may produce actual deficits of sodium either through renal or extrarenal losses as in vomitus and sweat, even though edema persists. This is obviously a serious complication since it leads to further circulatory deterioration. This form of hyponatremia is usually difficult to distinguish from the equally serious hyponatremia mentioned earlier and often a trial of sodium administration is required for differentiation (19b, c) (fig. 13-2). Again, as in other conditions of sodium depletion, it should be pointed out that the presence of normal or elevated levels of sodium does not exclude the existence of a low-salt syndrome. This is a disturbance in regional distribution of the body fluids: a systemic sodium depletion in the presence of peripheral edema (see fig. 8-6).

Finally, a word concerning the chloride ion in relationship to the changes in sodium: the level of this electrolyte alone or in conjunction with the bicarbonate level may reflect changes in sodium. This is not invariable and, as a matter of fact, is all the less likely to be true in severe congestive heart failure (see above, Section III, B, and fig. 13-3).

## V. Treatment of Congestive Heart Failure

As in all clinical situations extra burdens such as rheumatic myocarditis, thyrotoxicosis, and congenital or acquired abnormalities should be removed. However, in the common forms of this syndrome occurring in arteriosclerotic, rheumatic, or hypertensive heart disease the problem resolves itself into reduction of exertional activity so that it falls within the compass of cardiac ability while the efficiency of the myocardium is being raised to maximal levels. This means diminished labor as well as digitalis administration. Whether the latter exerts its beneficial effects by direct stimulation of the myocardium, or less directly, by lowering tachycardia or by decreasing venous tone and thereby permitting myocardial function within the

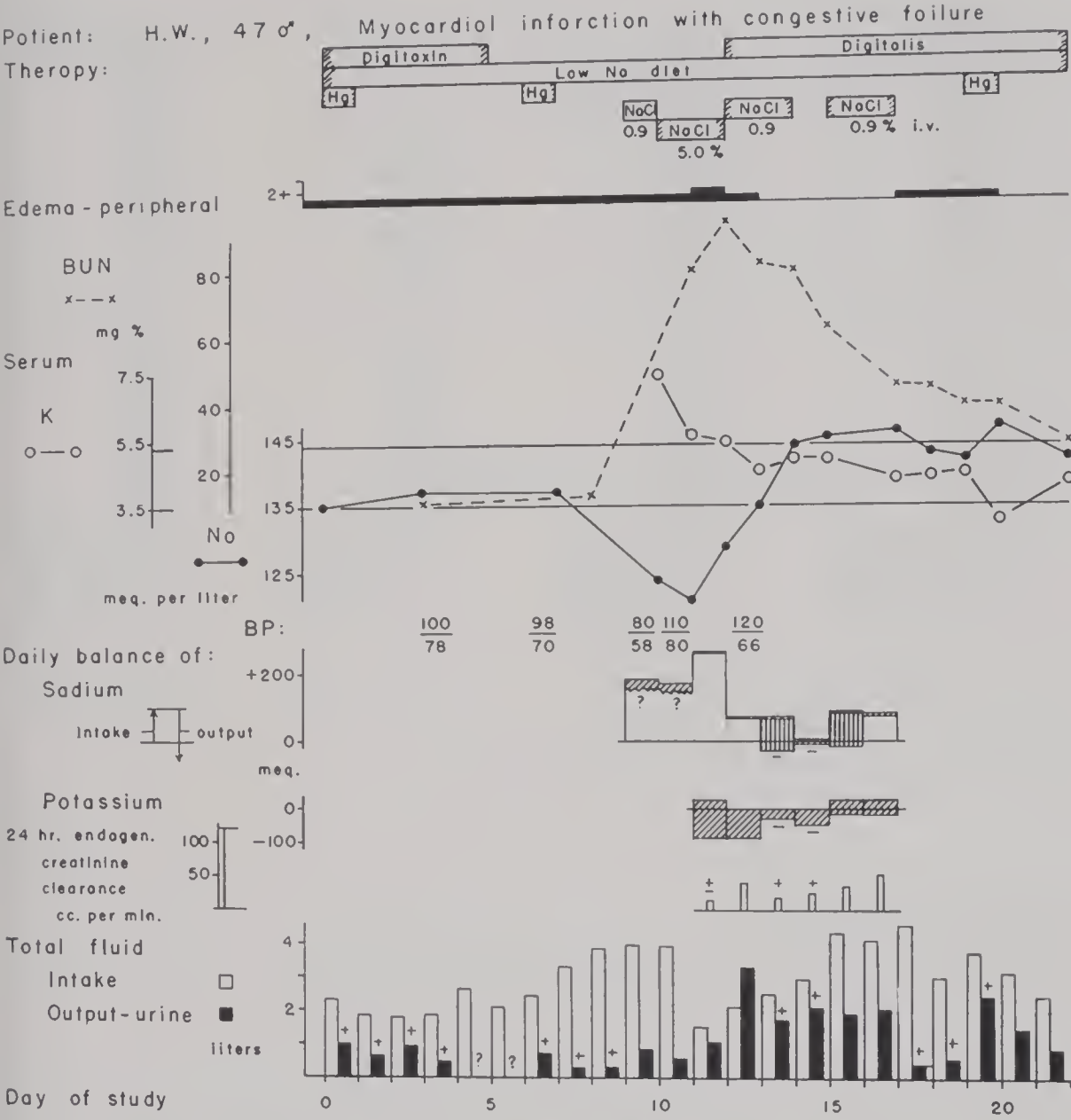


FIG. 13-2. RESPONSE OF A CARDIAC PATIENT WITH THE SALT DEPLETION TYPE OF "LOW SALT SYNDROME" TO HYPERTONIC SODIUM CHLORIDE SOLUTION

During the oliguric phase when the fluid intake was increased, days 8 to 11, the patient was hypotensive, the serum sodium level fell, and azotemia rapidly developed. On day 12 severe limitation of water intake plus hypertonic sodium therapy resulted in a rise in serum sodium concentration to 129 mEq./l. and a moderate increase in urinary output. On days 13 to 15 when water intake was moderately restricted but no hypertonic salt was given, the patient excreted a large volume of water with very little salt, resulting in the loss of edema and a restoration of the serum sodium concentration to high normal levels. This readjustment occurred without the retention of potassium. Subsequently the blood urea nitrogen returned to normal levels. (From Elkinton *et al.* (19c).)

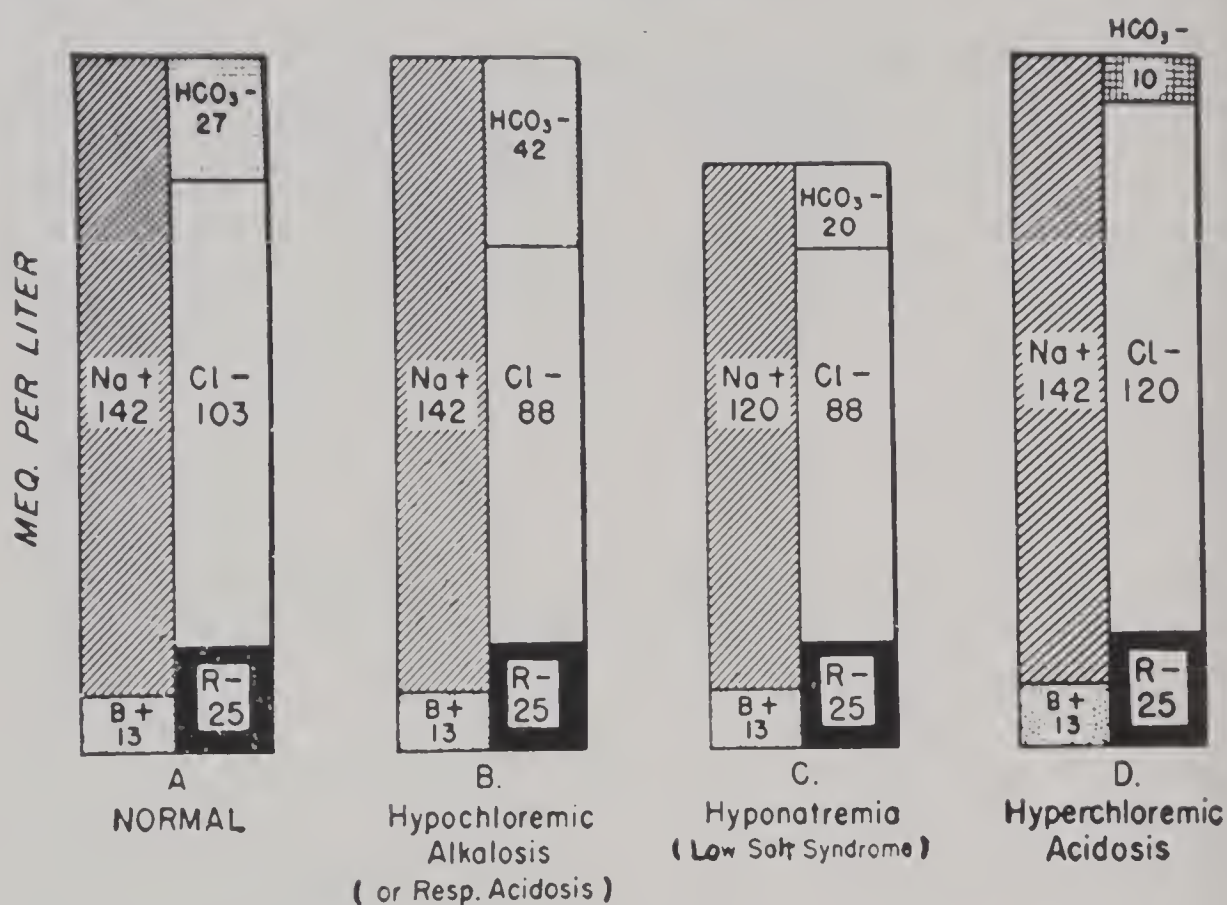


FIG. 13-3. ANION-CATION PATTERNS ENCOUNTERED IN CARDIAC OR CARDIOPULMONARY PATIENTS

B<sup>+</sup> stands for cations other than sodium and R<sup>-</sup> refers to anions other than HCO<sub>3</sub><sup>-</sup> and Cl<sup>-</sup>.

In column B hypochloremic alkalosis resulting from undue loss of chloride as in prolonged mercurial therapy, or occurring as a manifestation of cellular potassium deficiency is shown to be indistinguishable *without pH measurement* from primary respiratory acidosis.

In column C changes present in the low salt syndrome on the basis of either sodium and chloride depletion or the institution of a new steady state as a consequence of alterations in volume and concentration regulation are shown.

In column D the effects of NH<sub>4</sub>Cl therapy are shown. (After Schwartz and Relman (19b).)

limits set by Starling's law, is of minor import. It is essential, however, that enough digitalis or its products be given to meet the patient's needs rather than to satisfy a mathematical formula which was offered only to give the clinician some idea of orders of magnitude. This may necessitate producing digitalis intoxication in some patients before the therapeutic trial can be considered adequate.

The following principle holds with respect to eliminating the excesses of body water and sodium and preventing their reaccumulation: a negative balance of these elements must be achieved either by increasing the urinary output, decreasing the intake via the gastrointestinal tract, or both. Digi-



Patient: G.B., 39 y N, Chronic rheumatic heart disease

Therapy

K ocet

K acetate  
Hg  
50 gm./day

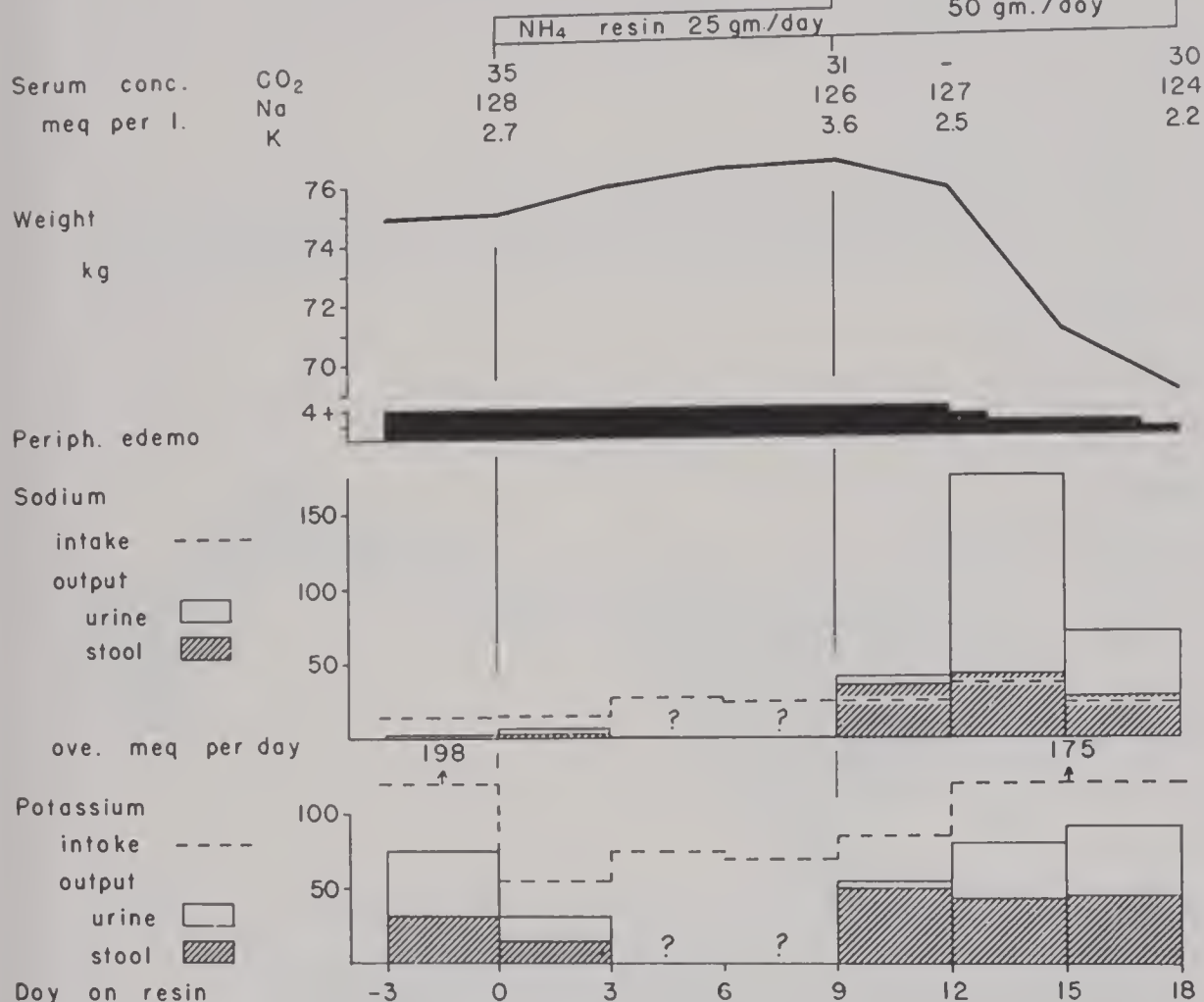


FIG. 13-4. RESIN THERAPY IN CONGESTIVE HEART FAILURE

The administration of a mercurial diuretic after the institution of cation exchange resin therapy resulted in the partial elimination of edema which had previously been refractory to mercurials alone. During days 10 to 18 inclusive, sodium was lost in the stools in amounts equal to or slightly in excess of the oral intake, but the largest portion of sodium was excreted in the urine. (From Elkinton, Squires, and Klingensmith (21a).)

talis and limitation of activity may effect the increased output; diuretic agents such as urea, ammonium chloride and similar acidifying salts, carbonic anhydrase inhibitors, and even a larger water intake may initiate or augment this increase. The decreased intake can be achieved by dietary restriction or the use of cation exchange resins. These therapeutic agents have all been discussed in detail in chapter 9. Their effects are illustrated in figures 13-4 through 13-8. However, it might be well again to point out the need for NH<sub>4</sub>Cl in patients who develop hypochloremia and alkalosis together with refractoriness to mercurial diuretics (18c, 19b, c). In such instances

Patient: S.B., 56 ♂ N, Congestive heart failure.

Therapy:

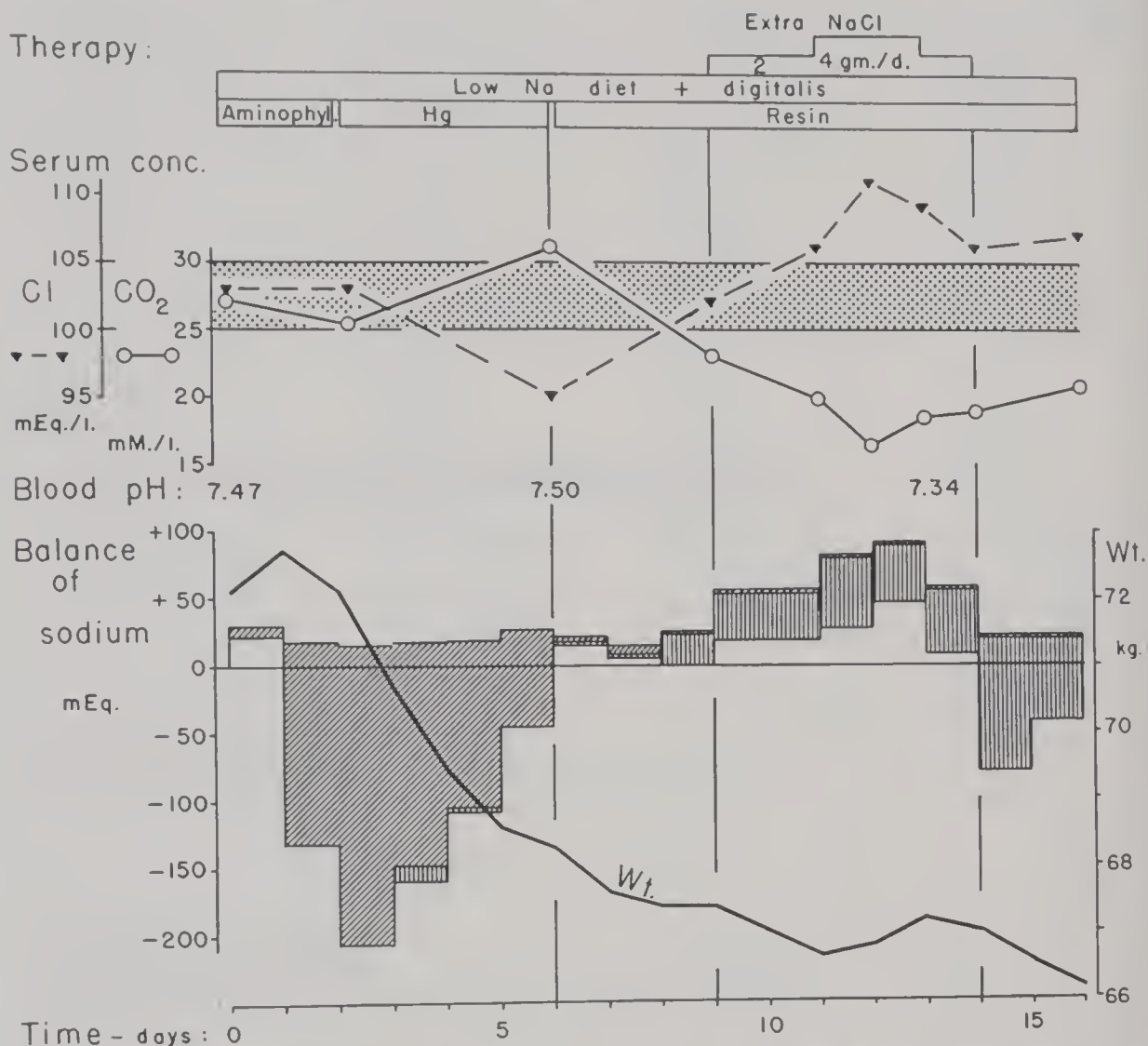


FIG. 13-5. TREATMENT OF CONGESTIVE HEART FAILURE WITH AMINOPHYLLINE, MERCURIAL DIURETIC, AND RESIN; LIMITATIONS IN THE ABILITY OF THE RESIN TO HANDLE EXTRA SODIUM CHLORIDE IN THE DIET

Intake is plotted upward and output downward; resultant above the zero line is a positive, and below a negative, balance. Urinary output of sodium is represented by diagonal crosshatching, fecal output by vertical lining.

Increments to the diet of two and four grams NaCl per day (days 10 to 14 inc.) resulted in a positive sodium balance and a metabolic hyperchloremic acidosis, i.e. the resin in the feces could not control the extra sodium nor the kidneys the extra chloride. (From data of Bluemle *et al.* (21b).)

restoration of chloride concentrations again permits the mercurial ion to serve as a natriuretic agent; carbonic anhydrase inhibitor may assist such a regime (19d).

The most difficult cases, as indicated earlier, are those instances of intractable edema which develop hyponatremia not attributable to sodium depletion. Restoration of cardiac efficiency is the main goal in these patients since by and large other measures are not successful. Weston and his col-

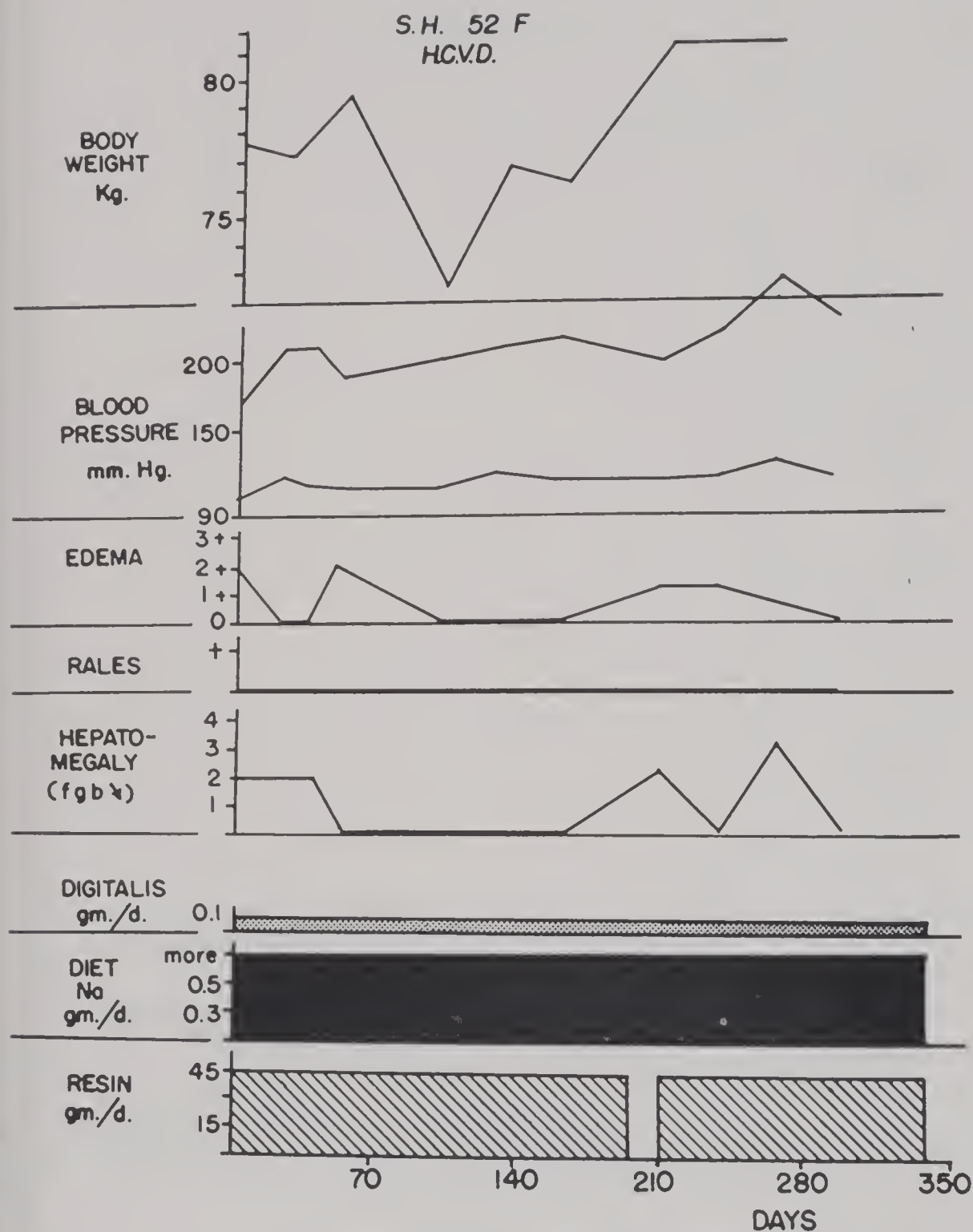


FIG. 13-6. CATION EXCHANGE RESIN THERAPY IN CONGESTIVE HEART FAILURE

S. H. was started on 45 grams per day of the  $H^+$ ,  $K^+$  forms of the cation exchanger. Sodium restriction was irregular and consisted of partial elimination of the salt shaker. She developed temporary gastric distress for two days after starting treatment and complained of constipation, but preferred the present therapy to the injections. She discontinued the resin on the 147th day because she had used up her supplies. When she was seen two weeks later, she had recurrence of her edema and hepatomegaly. These findings disappeared promptly when resin was restarted. She has been on treatment for 335 days at present. Her complaints have included paroxysmal dizziness and occasional blacking out. These events had occurred before resin was instituted however. (From Greenman, Shaler, Danowski (18c).)



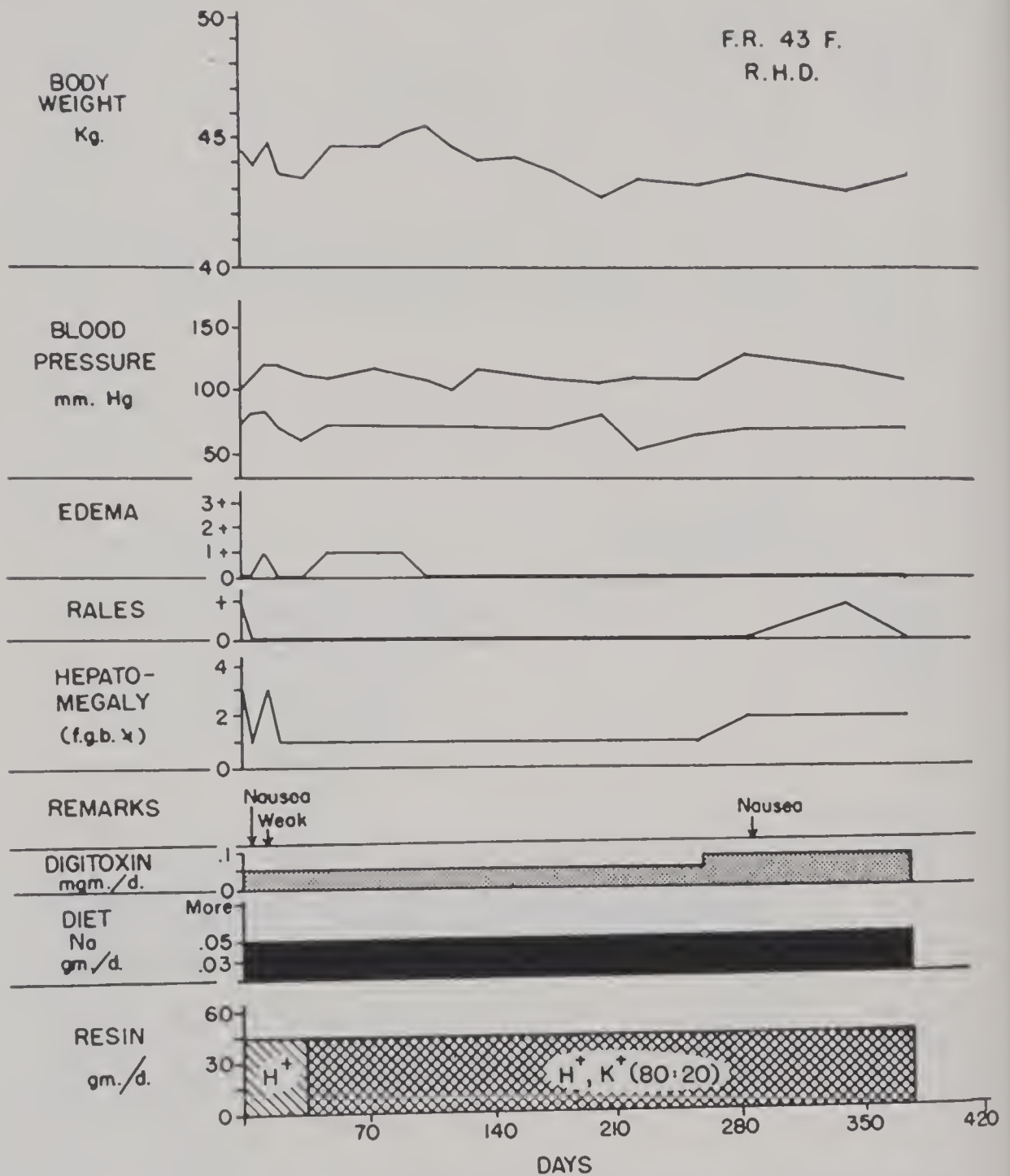


FIG. 13-7. EFFECTIVENESS OF PROLONGED CATION EXCHANGE RESIN THERAPY IN EDEMA

R. R. reported nausea, weakness, listlessness, constipation and bloating after the resin was started. In several days the nausea had disappeared and her only complaints were constipation and bloating. She received the  $H^+$  form of the resin for 35 days and then was placed on the combination of  $H^+$  and  $K^+$  forms. She prefers to take the resin for six days a week since she believes this prevents many of her gastrointestinal complaints. On the 259th day the digitoxin was increased to 0.2 mg. every other day and on her last visit to clinic she had no intestinal difficulties. (From Greenman, Shaler, and Danowski (18c).)

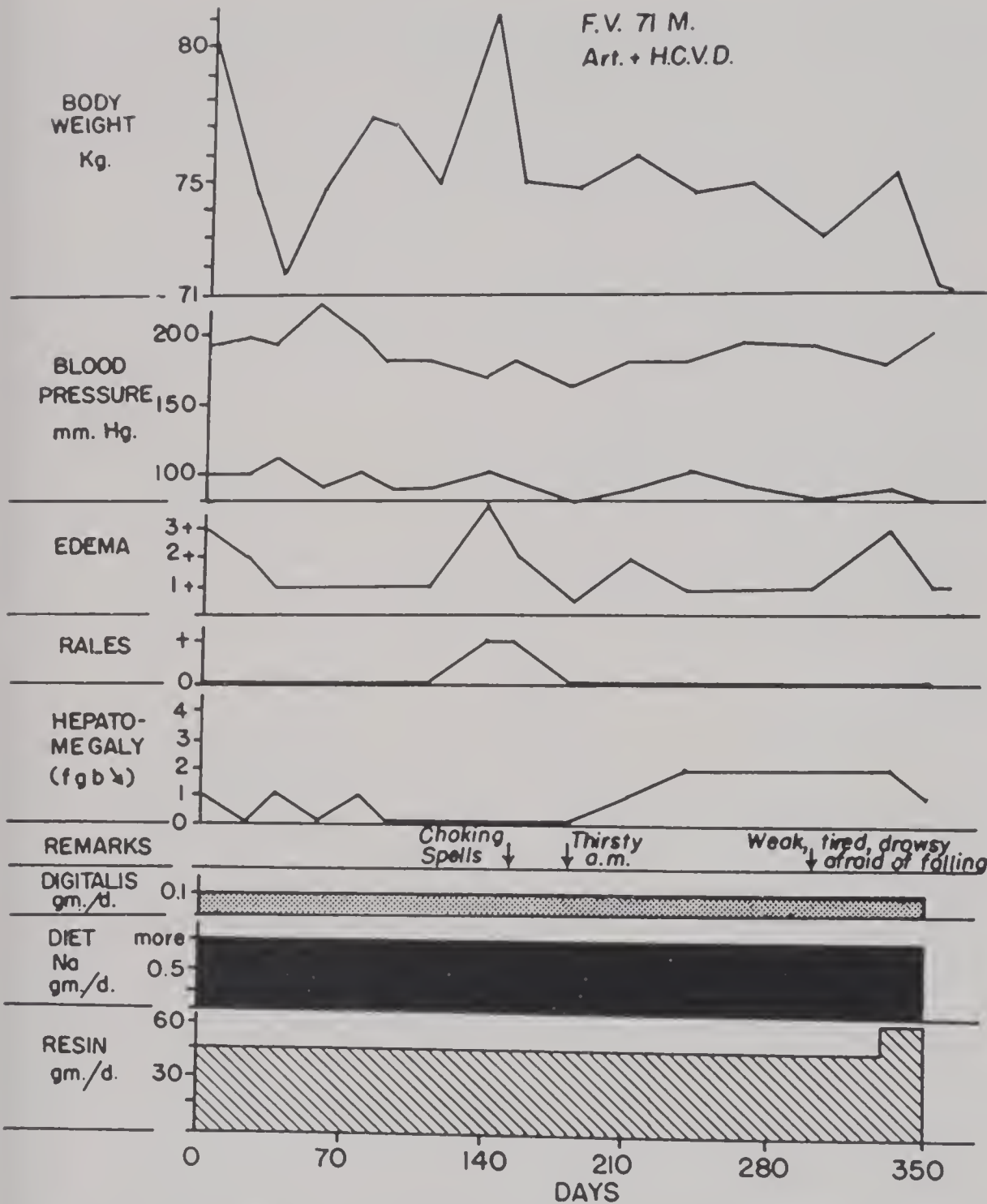


FIG. 13-8. HYPOKALEMIA DURING PROLONGED CATION EXCHANGE RESIN THERAPY

F. V. was started on 45 grams per day of the  $H^+$ ,  $K^+$  forms of the resin. The patient refused a low sodium diet but did reduce the use of the salt shaker. The resin produced slight gastric distress temporarily. On the 135th day the patient temporarily reduced his resin intake by half. On the 335th day his edema had again increased so the resin was raised to 60 grams per day. This was followed by a large diuresis with delivery of almost all the extra fluid, increased weakness, difficulty in walking and drowsiness. The serum potassium was abnormally low at this time and he was given supplementary potassium citrate, 6.0 grams per day for five days without clinical change but with elevation of his serum potassium to 3.6 mEq./l. (From Greenman, Shaler, and Danowski (18c).)

leagues report success in some of these patients with a regimen of potassium, extra digitalis, ammonium chloride, mercurial diuretics, aminophyllin, and cation exchange resins given within a period of one or two days in the order listed (20). As a final desperate measure hypertonic (3 to 5 per cent) NaCl solution should be given with restriction of total water intake, since in a minority of patients this sometimes leads to a diuresis.

In essence therefore we have presented a view of congestive heart failure in which the known alterations in the body fluids more or less characteristically present in such patients reflect alterations in the homeostatic regulation of amount, concentration and distribution of water and electrolytes within the body. Many factors, known and unknown, contribute to these new equilibria. The fact that patients may respond to judicious alterations in sodium metabolism or to other therapeutic measures should not distract the clinician from the realization that the fundamental cause of congestive failure is cardiac debility, relative or absolute. Every attempt should be made therefore to remove the *cause* of congestive failure, i.e., the disparity between the work load imposed on the heart and the work capacity of this organ, prior to manipulations of the *manifestations* of congestive failure.

**SUMMARY:** Irrespective of whether the edema of heart failure is taken to represent a renal inability to excrete sodium (i.e., forward failure) or is looked upon as a circulatory disturbance in which the Starling law concerned with hydrostatic and oncotic pressures is operative (i.e., backward failure), it essentially represents a disturbance of the mechanisms which regulate the volume, the distribution, and frequently, the concentrations of body fluids. As a consequence of such disturbances new steady states or equilibria are set up in which the total amount of body water and sodium is increased, the absolute and relative volumes of plasma, interstitial and cell fluid are altered, and the ionic composition may be changed inside and outside of cells. Though therapy is often directed toward the manifestations of congestive heart failure such as the edema, dyspnea etc., the key position of the heart in the genesis of these manifestations is well established. In view of the latter, the treatment of symptoms and manifestations must run *pari passu* with therapy designed to remove the disproportion between the need of the tissues with regard to oxygen and other forms of transportable materials, and the ability of the heart to meet such needs.

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## Chapter 14

### CIRRHOSIS AND ASCITES

#### I. Electrolyte and Water Changes in Cirrhosis

The progressive displacement of liver parenchyma by fibrous tissue ultimately produces comparable changes in most of the body solutes and fluids under discussion in this text, irrespective of whether the cirrhosis is of the biliary or Laennec's type.

##### A. *Early Changes in Body Fluids*

There are no adequate data to exclude the possibility that in the earliest phases of chronic progressive liver disease the body water and the chief electrolytes are appreciably altered, though still within the range of normal. In the presence of normal concentrations and in the absence of edema or ascites the total amounts are of course unchanged. As the disease progresses serum albumin falls and globulin rises. The first of these changes is commonly taken to reflect the inability of the liver to manufacture enough protein but it may well reflect the establishment of a new homeostatic level in response to other factors in the disease state. It is interesting in this regard that the disappearance rate of tagged albumin is decreased (1a, b). The etiology of the hyperglobulinemia remains unidentified.

Lipid changes in serum should be mentioned for the sake of completeness even though only the free fatty acids fall into the electrolyte category. In the early phases of Laennec's cirrhosis total cholesterol and lipid phosphorus values may be normal or low, whereas in obstructive jaundice marked increases are usually present. In addition in both entities the proportions of esterified and free cholesterol are changed. Ordinarily about 30 per cent of the cholesterol is in the free form. This increases as liver dysfunction interferes with the formation or persistence of cholesterol esters (1c, d).

The possible effect of high lipid concentrations upon the levels of electro-

lytes should be mentioned. It has been found that in entities such as diabetic acidosis or nephrosis extremely high levels of blood fat were associated with lowered electrolyte concentrations (1e). This is in a sense an artefactual result since in terms of concentrations of electrolytes in water the values were not necessarily abnormal. An aliquot of such serum or plasma contains an excessive amount of fat which occupies space but does not serve as a solvent for the electrolytes.

### *B. Electrolyte and Water Changes in Far-Advanced Cirrhosis*

In the far-advanced phase, i.e., in patients with ascites and edema, both the levels and total amounts of water and of solute are altered. In the uncomplicated cirrhotic of this type the total amounts of sodium and chloride are increased while their concentrations in serum are frequently lowered. The potassium levels are either normal or decreased while the bicarbonate may be decreased (fig. 14-1). As in the earlier phases albumin is down and globulin up, though to more pronounced degrees. The total and non-ionized calcium is lowered in keeping with the diminished albumin. The phosphorus in serum is not markedly changed (1f-h). In far-advanced cirrhosis the total lipid values tend to decline in both the biliary and Laennec's forms of the disease. The ester fraction continues to be abnormal (1d). A comparison of the fasting electrolyte levels in the far-advanced categories of cirrhotic patients, with and without ascites, based on unpublished studies from these laboratories, is presented in figure 14-1.

In an earlier chapter, number 4, it was pointed out that in human adults serum electrolyte levels are somewhat different in the two sexes. Thus, bicarbonate levels are known to be higher and the chloride levels lower in the males. In cirrhosis abnormal levels of estrogens accumulate largely and perhaps entirely as a result of the hepatic insufficiency. Gonadotrophins are lowered and the testicular output of 17-ketosteroids declines (1i-k). These changes are accompanied by testicular atrophy, breast enlargement, decreases in axillary hair, palmar erythema, and cherry nevi. In keeping with these evidences of "feminization" it is not surprising to find that the serum electrolytes in some of the members of this group of male cirrhotics had assumed a female pattern, i.e., with the chloride higher and bicarbonate lower than in the male. This is evident in figure 14-1.

## **II. Factors Operative in the Ascites, Edema and Sodium Retention in Cirrhosis**

The first thought that the ascites of cirrhosis is solely and directly a manifestation of the lowered serum albumin levels and increased portal vein pressures does not hold up under closer scrutiny. The chief arguments against this simple relationship is the repeated clinical demonstration that



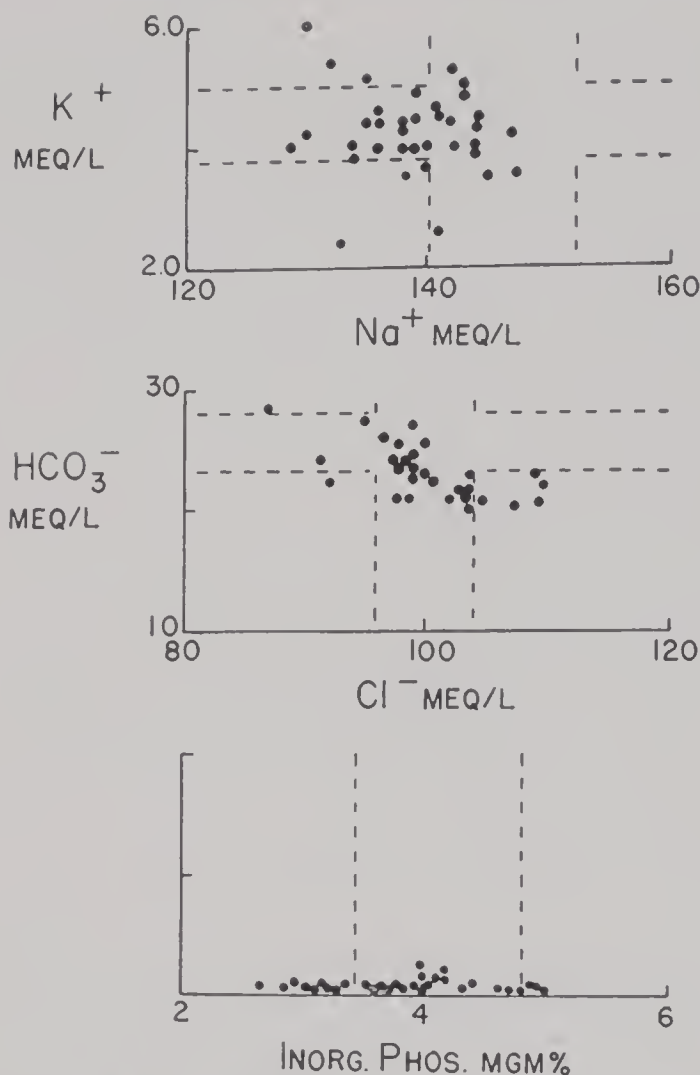


FIG. 14-1. FASTING SERUM ELECTROLYTES IN ADULT MALES WITH FAR-ADVANCED LAENNEC'S CIRRHOSIS

The dashes identify the range of values, mean  $\pm$  2 S.D., obtained in 60 to 64 analyses in healthy young adults. Open circles refer to patients with ascites. A tendency to hyponatremia is readily evident whereas the potassium levels are generally normal. As indicated in the text, the bicarbonate and chloride values have in many instances assumed the female pattern. The serum inorganic phosphorus is not usual. (Danowski *et al.*, unpublished data.)

plasma and plasma substitutes do not necessarily correct these abnormalities and that edema and ascites can be made to disappear without any discernible change in either the proteins or the pressures. However, even though there is no "critical level" of serum albumin at which edema invariably appears, it is true that the rates of transudate formation and reabsorption are altered in conformance with the differences in the hydrostatic and oncotic pressures (2a-d). It is only when the net effects of these exchanges result in an increasing peritoneal or subcutaneous fluid volume that ascites and edema appear. One factor in such net effects is the retention of sodium.

### *A. Sodium Metabolism in Cirrhosis*

As in the case of patients with congestive heart failure it has been shown that the fluid retention which occurs in cirrhotics arises in part at least from a restricted ability to excrete administered or ingested sodium (3a-d). A number of changes have been identified to be of potential or actual significance in this retention. Again, the question of the importance of a reduced glomerular filtration rate in limiting sodium excretion has been raised. As in the instance of certain congestive failure patients, it has been found that in cirrhosis glomerular filtration may be normal, and hence sodium retention has to be attributed in at least these patients to increased tubular reabsorption (4a-d). Increased tubular reabsorption of sodium has also been noted in experimental conditions which duplicate in part conditions which prevail in the cirrhotic once ascites has developed. Thus, increases in intra-abdominal pressure brought about by external constriction lower the excretion of sodium; also, as mentioned in the chapter dealing with congestive failure, increases in renal vein pressure interfere transiently with the renal output of this ion (5a-c). Both of these situations could and probably do occur in ascites.

### *B. Balances of Water in the Far-Advanced Cirrhotic*

The net positive balances of sodium which occur in cirrhosis are accompanied by a retention of water. The proportion of retained water to retained sodium is such however that the sodium levels are often at the lower distribution of values seen in healthy adults, or actually below it. There are at least four possible reasons for this disproportionate retention of water.

First, it may represent a change in the osmotically active components within cells. It has been shown that these can vary in amount (6a, b) and suggested that the generalized hypotonicity seen at times in chronic disease states such as tuberculosis (6c, d) could result from a decrease in cell solutes. A change such as this occurring in cirrhosis, possibly mediated through malnutrition, could account for the hyponatremia.

Second, the drop in sodium could indicate a form of sodium depletion produced by a combination of sodium restriction, mercurial diuresis, sweating, losses of the electrolyte via paracentesis abdominalis, etc. (7a-c). Though sodium depletion does occur in patients with cirrhosis and ascites it is not the commonest cause of hyponatremia. The chief proof for this is the observation that sodium administration usually does not prove beneficial but rather produces thirst and increased edema.

Third, the low sodium levels could represent an abnormal production or an undue survival of the posterior pituitary antidiuretic substances with a resultant over-retention of water and a dilution of the body fluids. Against

this is the observation that such patients often but not always respond normally to water loading and that the diuresis which follows ingestion of water can be interrupted with exogenous pitressin just as readily and as effectively as in normals (8a-e). These observations suggest that the onset of antidiuretic activity, its peak, and its duration are normal irrespective of whether the test situation is based on exogenous or endogenous pitressin. The finding of increased antidiuretic material in urine or in body fluids of such patients has in the past been advanced as an etiologic factor in the body fluid disturbances of cirrhosis (9a, b). Further studies with a precise technic indicate that this may indeed be true but that it may or may not be associated with edema and that comparably high elevations may be present in diseases such as hypertension without any evidence of body water excesses (9b). It should be kept in mind however that the materials which are measured by means of these bio-assay technics have not been identified as products of the posterior pituitary.

Fourth, the body fluid disturbance in cirrhosis with ascites and hyponatremia could represent a resetting of the volume and osmoreceptors of the hypothalamus at lower levels with normal production and disposal of antidiuretic substances. A new steady state is set up in which body water is increased, sodium levels are lowered, urine volumes are small, and salt excretion is limited.

Though some comments have been made concerning the possible validity of each of these explanations, our information is as yet insufficient to ascribe the development of hyponatremia in cirrhotics to any one of these categories to the exclusion of the others.

### *C. Metabolism of Potassium in Cirrhosis*

It is obvious that patients with cirrhosis are candidates for potassium depletion. The illness itself is major and is often accompanied by anorexia and decreased potassium intake. Vigorous measures such as mercurial diuresis and exchange resin therapy to augment sodium excretion are usually superimposed. These procedures result in an increased urinary and fecal loss of potassium. Hence the existence of potassium deficits should always be suspected in far-advanced cirrhotics and replacement should be tried (1g, 10a-c).

### *D. Reversal of Diurnal Variation in Water and Electrolyte Excretion*

It has been found that the usual pattern of fluctuation in the output of water, sodium and potassium may be altered in cirrhosis. Instead of the daytime peak and a nighttime minimum, the sequence is reversed (8e, 11a,



b). It is probable that this is just another manifestation of the abnormalities of endocrine and other factors in the regulation of body fluids.

### III. Treatment of Fluid Retention in Cirrhosis

Some 15 years ago it was demonstrated that many of the patients with advanced cirrhosis and fluid retention benefited by high protein feeding (12a-d). This expanded the previous programs of therapy based on attempts at sodium restriction, mercurial or urea diuresis, plasma or whole blood transfusions, and paracenteses at intervals. In the succeeding years there has been no substantial change in these therapeutic measures, though refinements have been attempted and newer agents introduced in accordance with the general discussion in chapter 9. Thus, within the last five years a greater emphasis has been placed upon more rigid sodium restriction, utilizing diets containing only a few milliequivalents of sodium in each day's intake (13a-g). Care must be taken in patients on such regimens to avoid sodium depletion by virtue of extrarenal losses of the ion or its removal via repeated abdominal tapping. The possibility that the absorption of ingested sodium can be minimized and the fecal excretion of this ion increased by means of cation exchange resins has also been studied (14a-c). These investigations have shown that some patients are benefited by these agents provided that their use is combined with some significant measure of sodium restriction. Particular care must be taken to avoid the use of resins or exchangers precharged with ammonium, since these patients cannot tolerate these forms and actual hepatic coma may be precipitated. This is discussed in greater detail in Section IV of this chapter. Cation exchangers in the hydrogen form can however be used to produce an acidosis which may by itself induce a diuresis, or can be combined with mercurial diuretics. Ammonium chloride should of course not be given to these patients, though other acidifying salts can be tried. Of the newer diuretic agents the carbonic anhydrase inhibitors are a promising innovation, though clinical trials are limited (15a-c). The synthetic plasma protein substitutes such as dextran, polyvinylpyrrolidone, or oxygelatin can now be used in place of blood, plasma, or human albumin in raising the oncotic pressure. They by no means prove uniformly effective even when given in nonsaline vehicles (16a, b).

It is evident from this summary that none of the current practices are invariably successful in preventing the reaccumulation of ascitic fluid in cirrhosis, even though immediate therapy is probably more effective than it used to be. This has undoubtedly been an important factor in leading to trials of surgical procedures such as the implantation of the Cooney button which for awhile permits drainage of ascitic fluid into subcutaneous spaces. More recently portacaval shunts have been produced surgically with benefit in some but not all patients (17a, b).

#### IV. The Electrolytes in Hepatic Coma

An extremely ominous sign in the course of far-advanced cirrhosis is the development of gross tremors described as "flapping" in type, and stupor or coma. These neurologic changes are accompanied by abnormalities of the electroencephalogram. The syndrome usually ushers in the terminal phase of the disease. There are no evidences that the coma can be attributed to further abnormalities in the chief electrolytes or in the water of the body (18a).

With the advent of the cation exchange resins a new phase in the understanding of the origins of hepatic coma was inadvertently achieved. In attempts to control edema with these agents it was found that the ammonium form of the resin precipitated stupor and tremors which cleared following withdrawal of the exchanger. Similar changes could be produced by ammonium chloride as well as by compounds or foodstuffs which gave rise to this ion. This established the probable genesis of hepatic coma, i.e., an inability of the body, and of the liver in particular, to cope with the ammonium or ammonia load. This was reflected in higher levels of this or related compounds in the blood of such patients (18b-j).

In treating this complication of cirrhosis the most important goal should be the improvement in liver function by relying upon the older regimens as well as undertaking judicious trials of some of the newer agents such as the lipotropic substances, cortisone and ACTH (19a, b). Obviously ingestion of ammonium compounds as such or their precursors, and among the latter high protein diets must be included (19c), should be closely controlled. Vivodialysis by means of the artificial kidney is certainly worthy of trial in cases where medical management proves inadequate.

**SUMMARY:** The crucial water and electrolyte problem in cirrhosis of the liver is water and salt retention in the form of ascites and dependent edema. The fact that hypoalbuminemia may be present without ascites and edema, that ascites and edema can be removed without correcting pre-existing hypoalbuminemia, and finally, that restoration of colloidal osmotic pressure by plasma, albumin, or serum protein substitutes need not result in a delivery of edema indicates that other conditioning factors are operative in the undue retention of salt and water. Some of these have been identified. Thus, the renal excretion of sodium loads is diminished. The tendency for hyponatremia to develop in such patients with edema and ascites unassociated with sodium depletion points to disturbances of regulators of the volume and concentration of the body fluids. Therapy is directed at restoration of liver function and serum proteins toward normal by means of an optimal protein intake; symptomatic treatment with plasma expanders, diuretic agents, cation exchange resins etc. is to be undertaken with suitable pre-

cautions to avoid precipitation of hepatic coma as a consequence of "ammonia" accumulation.

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“Diabetes is a wonderful affection, not very frequent among men, being a melting down of the flesh and limbs into urine.”

Arætaeus the Cappadocian

## *Chapter 15*

### **DIABETIC KETOSIS AND COMA**

The effective and prompt disposal of carbohydrate loads requires insulin in adequate amounts. Since pancreatectomy is known to lead to mild diabetes which is readily controllable with 15 to 45 units of insulin each day, it is possible that anti-insulin factors are present in patients with spontaneous diabetes requiring larger daily amounts of this hormone. Such an anti-insulin effect could be mediated through changes in the insulinase-anti-insulinase system described by Mirsky and Broh-Kahn (1a, b). As summarized by Stadie (2a, b) relative or absolute deficits of insulin interfere with metabolism of carbohydrate at one or more sites: a) entry of glucose into cells and cell structures is impeded (2c, d) (see 1 in figure 15-1), b) the phosphorylation of glucose by means of glucohexokinase and adenosine triphosphate (ATP) is retarded (2e, f) (see 2 in figure 15-1), and c) the formation of new ATP and the conversion of pyruvic acid to  $\text{CO}_2$  and  $\text{H}_2\text{O}$  through the citric acid cycle (12g-i) (see 3 and 4 in figure 15-1) proceed at slower rates. Hormonal factors (anterior pituitary, adrenal cortex, and thyroid) also retard carbohydrate disposal (2j-m) but their sites of action are not known and their roles, if any, in the clinical entity of diabetes mellitus remain unclarified.

Diabetic acidosis and coma result in the last analysis from an insufficient amount of insulin. This can be a consequence of withholding insulin or result from a rise in insulin requirement produced by starvation, liver deglycogenation, hypoglycemia, infection, a decrease in physical activity, or from emotional disturbances (3a-i). Several sequelae appear upon interruption of the glycolytic cycle. Hyperglycemia is naturally one of the earliest. It is aggravated by conversion of liver glycogen to glucose, and by formation of sugar from other body components such as amino acids and glycerol. As the sugar level rises and the reabsorptive capacity of the kidney tubules is exceeded glycosuria appears.

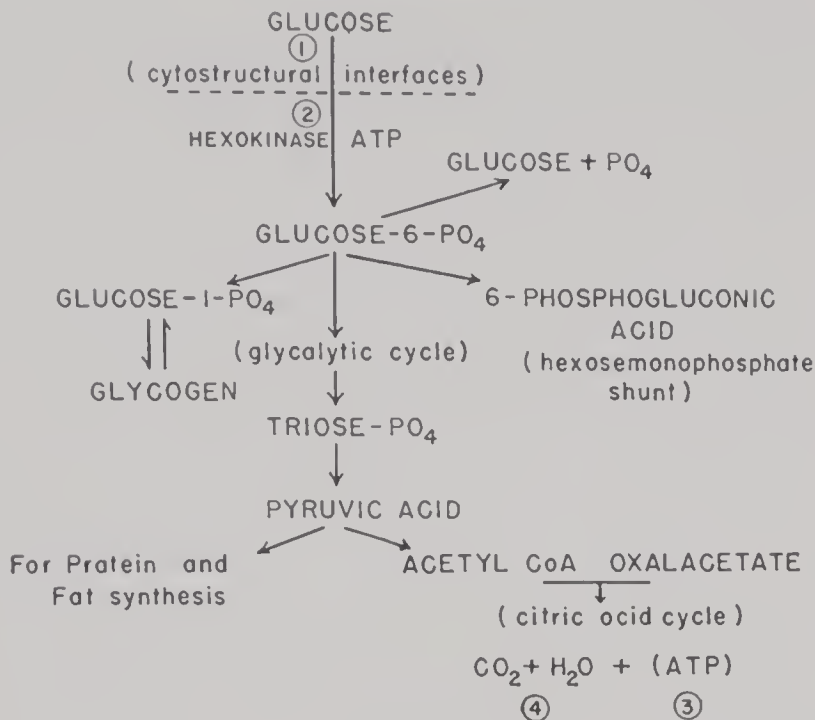


FIG. 15-1

#### METABOLIC PATHWAYS FOR DISPOSAL OF GLUCOSE AND POSSIBLE SITES OF INSULIN ACTION

The disposal of glucose involves entry into cells and formation of a phosphate ester. Thereafter, the phosphorylated glucose may be converted into glycogen, enter the 6-phosphogluconic shunt or proceed to pyruvic acid via the glycolytic cycle. Pyruvic acid may in turn give rise to active 2-carbon fragments for the synthesis of protein and fat (the so-called proteogenic and lipogenic action of insulin) or enter the citric acid cycle where it is converted to  $\text{CO}_2$  and  $\text{H}_2\text{O}$  and the energy is utilized to form ATP. In diabetes mellitus penetration into cells (see 1 in above figure), formation of glucose-6- $\text{PO}_4$ , conversions in the citric acid cycle, and formation of ATP are decreased and represent possible sites of insulin action (see 2, 4, and 3 in above figure). (Modified from Stadie (2a, b).)

Insofar as the metabolism of foodstuffs is concerned the organism shifts to fat utilization with the interruption of glucose catabolism. In the absence of a protein intake and adequate carbohydrate metabolism negative balances of cell nitrogen develop. Fat is mobilized and converted in the liver to ketone bodies which are then utilized by cells for energy purposes via metabolic pathways which do not require insulin. They are, however, produced in excess of the capacities of tissue utilization and renal excretion and accumulate as unmeasured anions in the body fluids (4a-c). This rise in the "x" fraction, or unmeasured anions, of the Gamble diagram is responsible in great measure for the metabolic acidosis which develops.

As the bicarbonate and other buffer anions decline, hyperventilation of the Kussmaul type appears. This stimulation of the respiratory center is a secondary response to the metabolic acidosis, and results in amelioration of the fall in pH by lowering the alveolar and arterial  $\text{P}_{\text{CO}_2}$ .



This, then, is the metabolic framework within which deficits of body fluids develop.

### I. Losses of Water in Diabetic Acidosis and Coma

Review of the clinical history of patients with this complication of diabetes reveals a high incidence of anorexia and vomiting (5a-e). In one of these series (5a) at least three-quarters of the patients gave such a history. Whether this is a manifestation of, or leads to, ketosis or acidosis is often difficult to determine. The end result is the same: interference with an adequate intake of water. In the face of this, body water is lost in vomitus and its usual rate of loss via urine and via the lungs is accelerated by virtue of glycosuria and Kussmaul overbreathing, respectively. As a consequence a net deficit of body water develops, accompanied as will be seen in the sections which follow, by deficits of body sodium and potassium.

### II. Losses of Sodium in Diabetic Acidosis

Sodium and chloride depletion is frequently present upon admission. This is attributable in some measure to losses in vomitus (fig. 15-2). It is

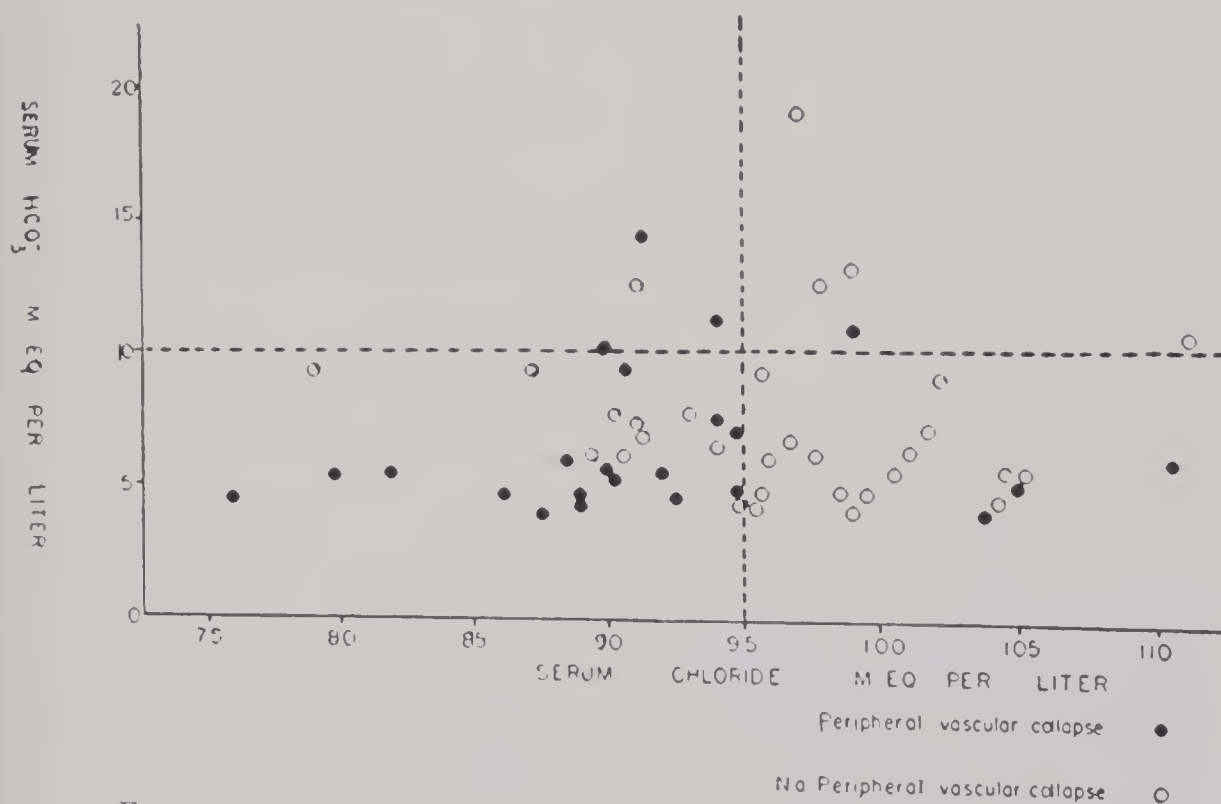


FIG. 15-2. RELATION OF HYPOCHLOREMIA TO PERIPHERAL VASCULAR COLLAPSE

Sixty-five per cent of the patients with a concentration of serum chloride on admission of 95 mEq./l. or less developed peripheral vascular collapse. Shock appeared in only 12 per cent of the patients with normal concentrations of serum chloride.

It is apparent that reduction in the concentration of serum bicarbonate without hypochloremia did not predispose to shock. From Danowski *et al* (5a).)

also likely that this negative balance is increased as a result of a continued urinary output of these two electrolytes. Though data on this point are not conclusive, it is probable that the usual conservation of sodium and chloride by the kidney in the face of an inadequate intake or deficiency of this ion is compromised by the glucose diuresis (6a-g). This appears to be true even though such patients or experimental subjects show other evidences of increased adrenocortical activity such as eosinopenia and increased amounts of 17-ketosteroids and glyconic corticoids in the urine (7a-f).

The sodium deficits, accompanied by chloride and water losses, understandably reduce the circulating plasma volume. The cardiac output, blood pressure, circulation time, and renal blood flow are adversely affected, and circulatory collapse with or without acute tubular damage of the lower nephron nephrosis type may develop (5a, 8a-g).

### III. Losses of Body Potassium

Without exception patients in acidosis or coma are in negative potassium balance. They have all been deprived of an adequate intake during periods of time when renal and extrarenal losses of this electrolyte are increased. The relatively high potassium content of gastrointestinal fluids accounts for the latter (6c, e, 9a-c) whereas increased urinary loss in a patient under stress is the final common pathway by which both extracellular and cell potassium are lost. The following processes contribute to the losses of cell potassium (10): a) deglycogenation releases potassium deposited in the liver, b) negative cell protein balances as a consequence of starvation and increased gluconeogenesis contribute another fraction of potassium, c) dehydration evokes a transfer of cell potassium to the extracellular fluid, and d) interruption of carbohydrate metabolism interferes with the energy conversions which serve to keep potassium inside of cells. These events have been discussed in detail in chapters 6 and 7.

### IV. The Blood and Serum Solutes and Electrolytes Prior to Therapy

In the early phases water is transferred from cells to the extracellular fluid in response to the increased osmotic pressure exerted by glucose. Subsequently dehydration, electrolyte transfers and circulatory changes modify this picture. Hence the duration of the pretreatment period will obviously influence the solute pattern. Certain general statements can however be made.

Most of the patients have azotemia. This stems in part from diminished clearance of urea on the basis of circulatory inefficiency with or without lower nephron nephrosis, but it should be remembered that the breakdown of body protein occurring in diabetic coma also presents a greater nitrogen load for urinary excretion.

The anion pattern is characterized by marked reduction in serum bicarbonate as a consequence of increased ketone bodies; in some instances diminished urinary function may produce rises in other components of the "x" portion of the Gamble diagram while in others a lowering of serum cations may be a contributory factor; pH measurements indicate this to be a metabolic acidosis. The chloride levels are usually lowered, though a concomitant deficit of water can mask the effects of chloride loss in vomitus; serum proteins may be elevated, again because of the water deficit; serum inorganic phosphorus is usually normal or elevated.

Of the cations, sodium levels are often decreased as a reflection of negative balances of extracellular sodium which develop. The concentration of potassium in serum is usually somewhat increased; this is marked in oliguric patients, but may be absent or an actual hypokalemia may appear in patients with marked diuresis, especially in children (11a-k). No significant changes have been described in the total serum calcium levels nor are any data available concerning the ionized fraction. Some of the patients have been found to have increased levels of serum magnesium (12a-c). Illustrative examples of some of these changes are shown in figures 15-3 and 15-4.

## V. Therapy of Diabetic Acidosis and Coma

The fundamental problems to be solved include: restoration of carbohydrate metabolism to normal, treatment of circulatory collapse, and correction of water and electrolyte disturbances.

### A. Restoration of Carbohydrate Metabolism

The *sine qua non* for resumption or acceleration of carbohydrate metabolism is insulin. This should be given promptly if possible, even before the patient is sent to the hospital; quick acting insulin should be used exclusively and in adequate dosage. In the initial phase of treatment at least some of it ought to be given intravenously to eliminate the delay due to absorption. Experience with both children and adults indicates that most but not all cases of severe acidosis or coma should receive 100 or 50 units of crystalline insulin on admission with 50 to 30 units each hour for the first four to six hours of therapy (11f, g, 13a-e). Thereafter, the levels of blood sugar, of bicarbonate in blood, and of ketone bodies in urine or in blood determine the dosage. Usually, the interval between injections is extended and the dosage reduced. The net experience indicates that this schedule will usually result in a total insulin dosage of some 200 units in the first 24 hours (5a).

Such a program will permit prompt restoration of the depleted liver gly-



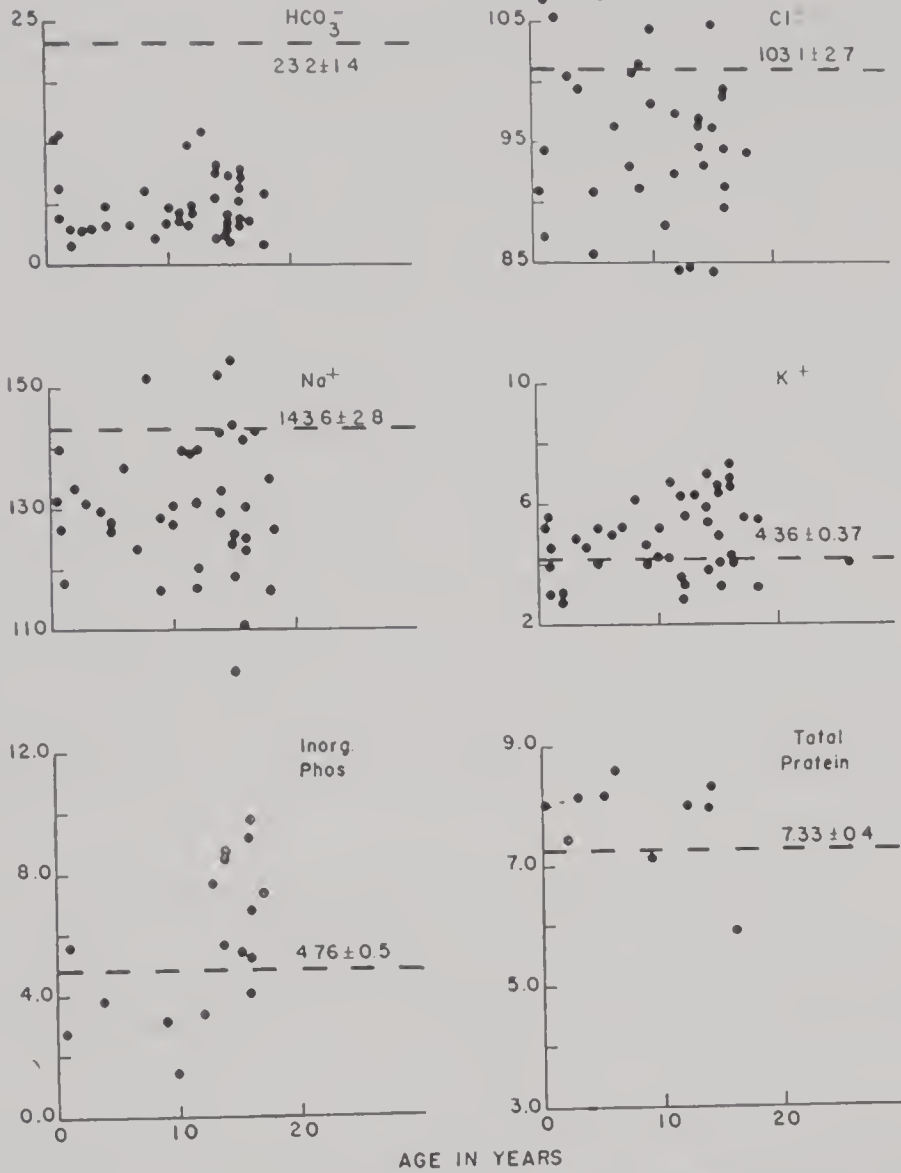


FIG. 15-3. SERUM SOLUTES IN DIABETIC ACIDOSIS OR COMA PRIOR TO TREATMENT

The broken line identifies the mean values,  $\pm 2$  S.D., found in determinations of the fasting serum levels in the particular electrolyte under consideration in 70 to 148 healthy nonhospitalized children 5 to 18 years of age. In diabetic acidosis a high incidence of hyponatremia and hypochloremia is present together with a tendency to hyperkalemia and hyperphosphatemia. The serum total proteins are also elevated above normal. (Danowski *et al.*, unpublished data.)

cogen stores to normal and thereby decrease the production of ketone bodies (13f-j).

### B. Treatment of Circulatory Collapse

At the same time the first insulin is given, or as promptly thereafter as possible, the patients should receive whole blood, plasma or plasma substitutes in treatment of the circulatory inefficiency or collapse which accompanies dehydration and electrolyte depletion. There are two reasons for this adjuration: first, in this way all patients who have circulatory col-

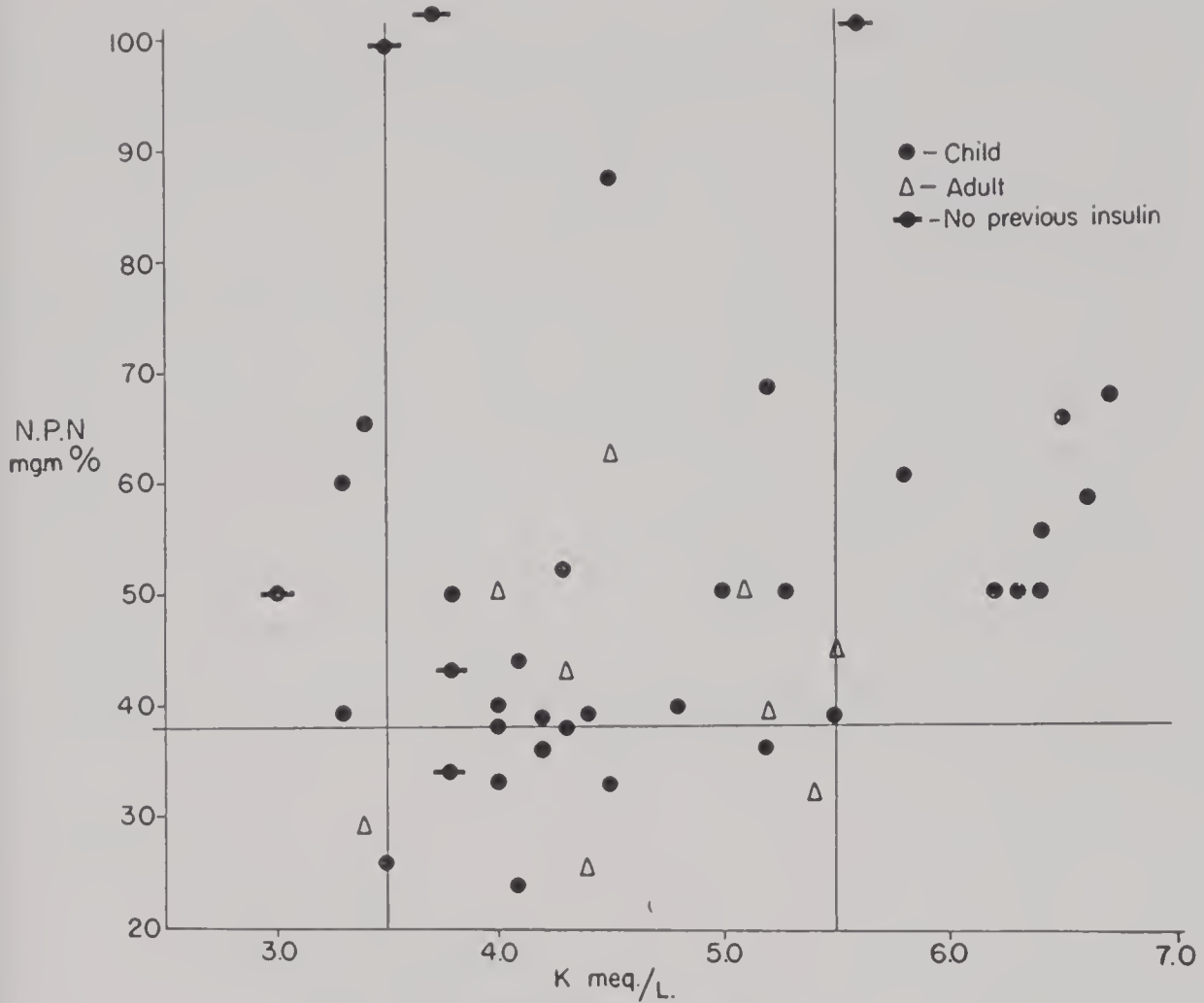


FIG. 15-4. SERUM K IN DIABETIC ACIDOSIS

This figure illustrates the relationship between serum potassium concentrations and whole blood NPN in 48 consecutive patients with diabetic acidosis prior to therapy. The upper limit of normal for NPN is indicated by the horizontal line through 38 mg. per cent and for potassium by the vertical lines. The number of cases in each category is depicted by the number inside the figure. The poor correlation of NPN and potassium is clear, but no patient with a high potassium level had a normal NPN. Serum potassium values were normal in the majority of the subjects, but NPN concentrations were elevated. Note the wide scatter of potassium in the children who had not received previous insulin. (Danowski *et al.*, unpublished data.)

lapse will be treated promptly whereas the others will not be harmed; second, the treatment of dehydration by replacement of water and electrolyte deficits is slow and the restitution of circulatory efficiency is incomplete. The use of these colloid agents provides prompt treatment of the diminished plasma volume and actually improves the response to saline when it is started (14a-b).

### C. Correction of Water and Electrolyte Disturbances

**1. Use of sodium-containing solutions, including lactate.** The deficits of water, sodium and chloride are corrected by infusion of 0.9 per cent

saline or Ringer's lactate during or following the colloid administration. In an adult some two to four liters should be given at the rate of 500 cc. per hour in the course of the first six to 12 hours for a total sodium chloride intake of 18 to 36 grams in one day. This is in keeping with the experience in the series of patients referred to earlier (13a-e).

Some comment is necessary concerning the use of 0.9 per cent saline since in some clinics Ringer's lactate,  $\frac{1}{6}$  molar lactate, or similar solutions are employed (15a-e). It is true that 0.9 per cent saline is not "physiological" in that it has 154 milliequivalents of sodium and of chloride per liter. These concentrations are higher than those present in health and certainly the proportion of sodium to chloride is not that in body fluids. It is also true that sole reliance upon this solution for replacement purposes will often produce undue elevations of the two ions and that the hyperchloremia may prevent the prompt restoration of body bicarbonate to normal. It is to be noted however that a limit can be set upon the volume of solution to be used. This permits quick replacement of body deficits of sodium and of chloride and partial replacement of body water. If administered in appro-

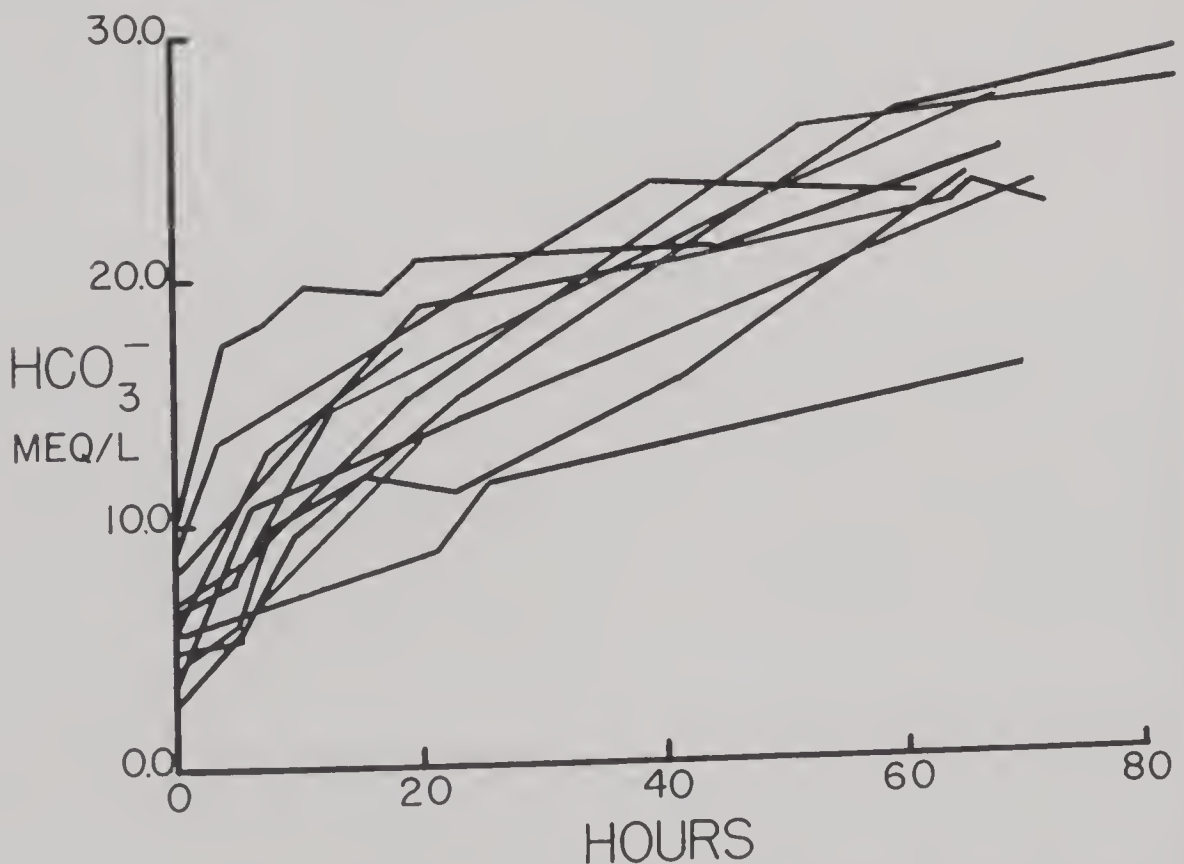


FIG. 15-5. PROGRESSIVE RISE IN SERUM TOTAL CO<sub>2</sub> CONTENT DURING THERAPY OF DIABETIC COMA WITHOUT ALKALI

The progressive rise in bicarbonate in these patients indicates a satisfactory response to insulin—saline—and, ultimately, glucose administration without use of alkali. In the severely ill patient with distinct pH change it is desirable to administer alkali immediately following admission. (From Danowski *et al.* (11f).)



priate amounts there will be no interference with bicarbonate rise and such a rise can be employed as an index of the metabolic response to therapy (figure 15-5). On the other hand Ringer's lactate or  $\frac{1}{6}$  molar lactate solution will obviate the use of the bicarbonate level for this purpose and minimize the replacement of chloride. However, the writers do not feel strongly about this preference. As a matter of fact, the lactate solutions are given to some of our severely ill patients in whom the pH is markedly lowered. The work of Guest and his collaborators indicates that in such patients a given amount of insulin will prove more effective in disposing of glucose when the acidosis has been corrected (15f, g).

It should be mentioned that in pediatric practice solutions which contain sodium, chloride, potassium, and metabolizable anion in concentrations which would render the total solution hypotonic if they were not dissolved in 5 per cent glucose, are often used. This is discussed in chapter 20 and the solutions are described in chapter 24.

**2. Role of aqueous solutions of glucose and other monosaccharides.** There are two reasons for the administration of glucose in water: 1) reliance upon saline or lactate mixtures will not completely cancel the

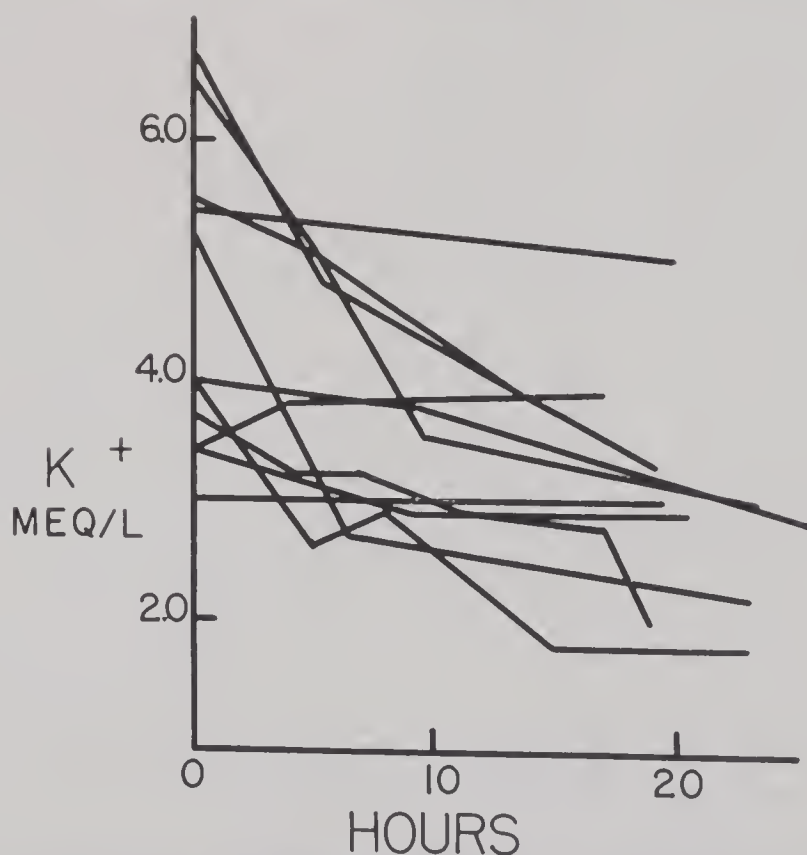


FIG. 15-6. PROGRESSIVE DECREASES IN SERUM POTASSIUM DURING THERAPY OF DIABETIC COMA

It should be noted that in these 11 children pretreatment levels were low, normal, or high and in general declined with the administration of saline and insulin. In adults the admission values are more regularly elevated. (From Danowski *et al.* (11f).)

deficits of water whereas the injection of glucose in water is ultimately the same as giving pure water, and 2) the administration of glucose, once the blood sugar has begun to fall, accelerates the utilization of carbohydrate, minimizes negative balances of nitrogen, and prevents hypoglycemia. This point of view has been discussed in detail by others elsewhere (16a-l).

Recently the possible usefulness in this regard of fructose, which does not require insulin for entry into the glycolyte cycle, has been studied. It has been found that the administration of fructose to diabetic patients results in a definite though limited increase in carbohydrate utilization without increase in insulin requirement (16m-o).

A word of caution concerning the route of administration of the glucose

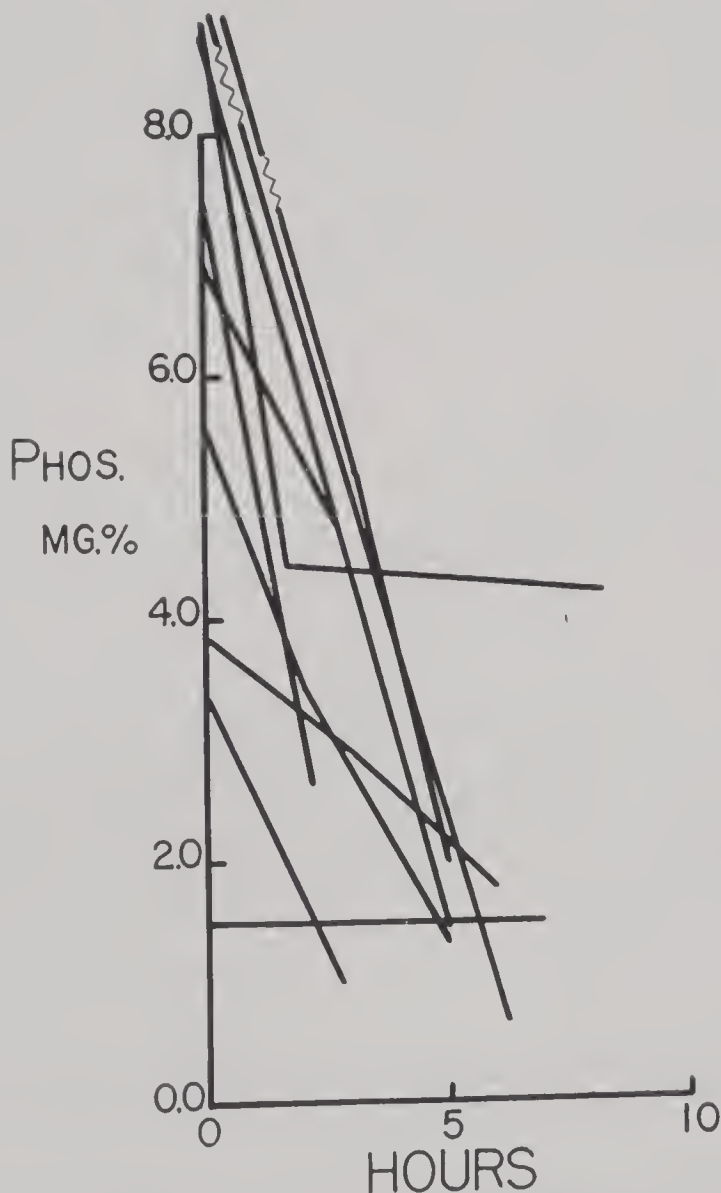
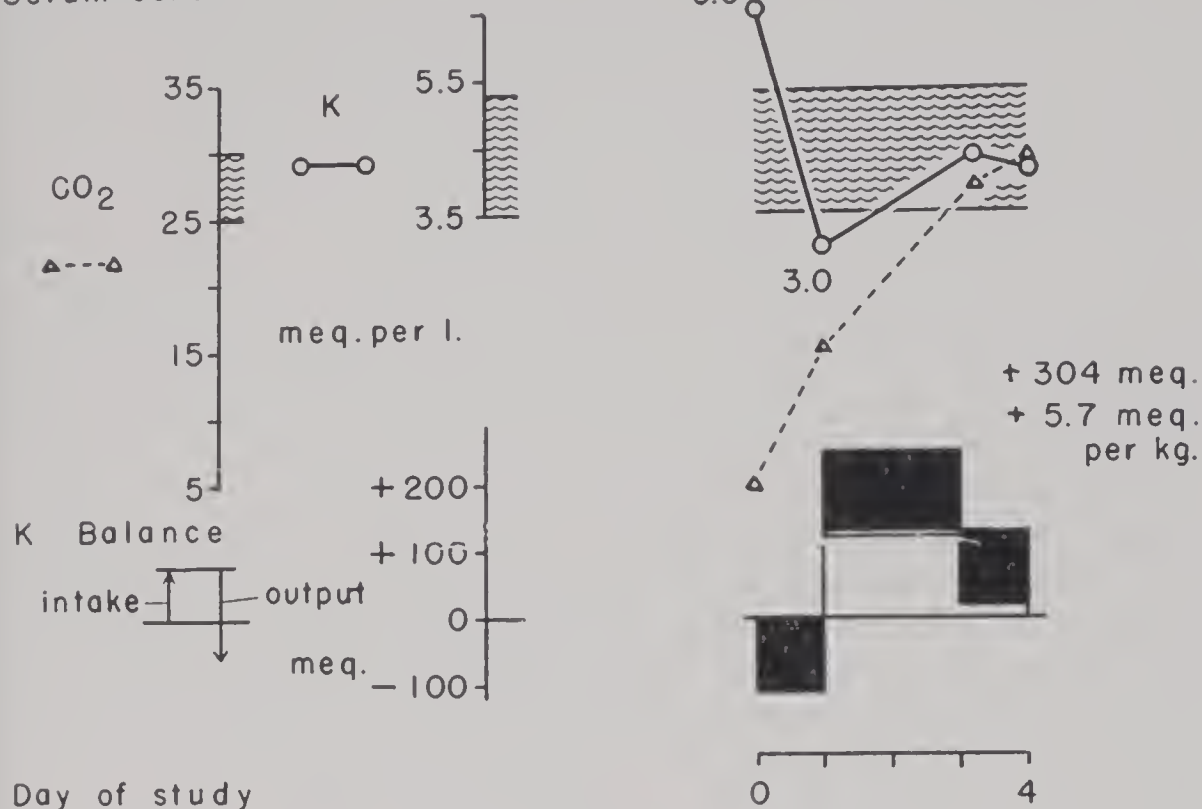


FIG. 15-7. CHANGES IN SERUM INORGANIC PHOSPHORUS DURING RECOVERY FROM DIABETIC COMA

In general the serum inorganic phosphorus declined from the high levels present on admission as recovery ensued during the administration of insulin and saline. (Danowski, *et al.*, unpublished data.)

Patient D.C (a) Diabetic acidosis  
Therapy

Serum conc.



Interpretation of serum concs

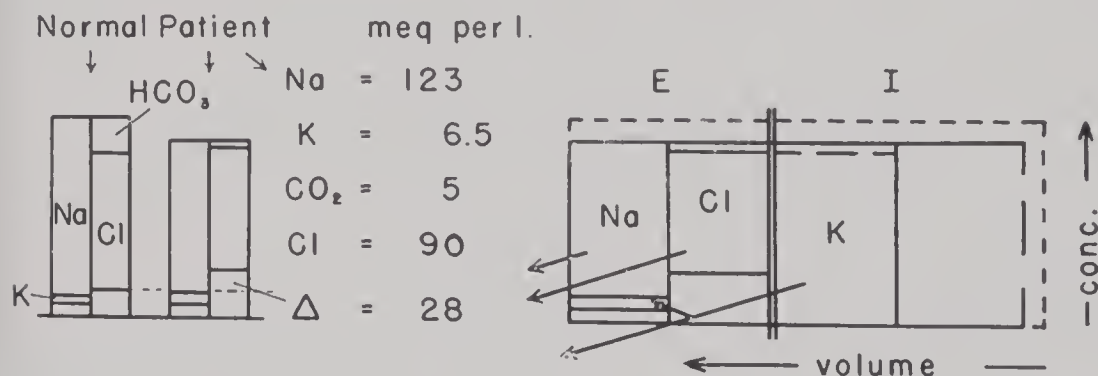


FIG. 15-8. BODY FLUID DISTURBANCES IN DIABETIC COMA. SERUM CONCENTRATION: HIGH POTASSIUM, LOW SODIUM, LOW CARBON DIOXIDE

Clinical data and diagnosis. D. C., a 16-year-old female in diabetic acidosis and coma, was treated with insulin and saline solutions, followed by milk diet plus potassium chloride by mouth, leading to positive potassium balance.

Interpretation of serum concentration at start of day one: *Body fluid pattern:* Extracellular deficit of sodium and chloride without diminution of volume of water, retention of ketones displacing bicarbonate (metabolic acidosis); intracellular deficit of potassium with extracellular excess of that ion (hyperkalemia).

*Physiologic mechanisms:* Sodium lost in urine as base associated with ketone acids and to some extent lost in vomitus. Potassium lost from intracellular phase owing to changes in carbohydrate metabolism, starvation and low potassium intake. Accumulation of potassium, in extracellular fluid as renal excretion became inadequate. The abrupt transition from hyperkalemia to hypokalemia during day one was due to increased renal excretion of potassium, expansion of extracellular fluid volume, and deceleration of transfer of potassium from cells. (From data of Danowski *et al.* (11f) as presented by Squires and Elkinton (20).)



or fructose solution is in order. It should not be given subcutaneously, since the pooling of this nonelectrolyte solution in the tissue spaces temporarily abstracts extracellular electrolytes (17). If this is superimposed on pre-existing sodium and chloride deficits, salt depletion shock can be precipitated. Hence, either the deficits should first be made up or the solution should be given slowly by vein.

**3. Use of potassium salts.** The replacement of body potassium should be started several hours following admission when it is certain that the urine output is adequate and that hyperkalemia is not present. This usually coincides with the beginning of a drop in the blood sugar level. The potassium must be given intravenously. The chloride or buffered phosphate salt can be used in concentrations of 20 to 60 milliequivalents per liter in five per cent glucose or 0.9 per cent saline. Approximately 500 cc. of such a solution can be given with safety, as has been stated, if urine flow is good and potassium levels in blood are normal or low. The appearance of peaking of the T wave in lead II of the electrocardiogram can be used as a danger sign of rising potassium concentrations, if determination of potassium levels by means of flame photometry is not readily available. The amount given

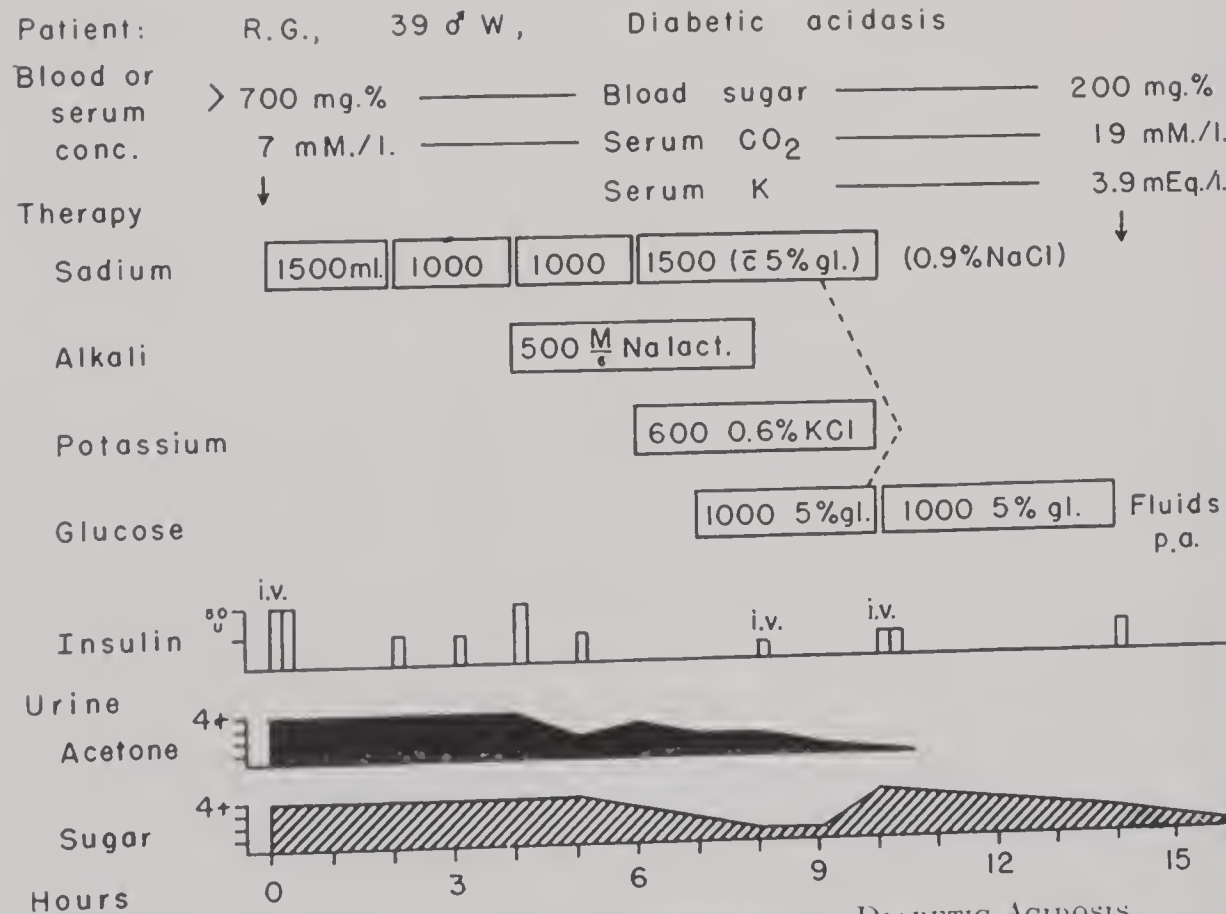


FIG. 15-9. TYPICAL COURSE OF TREATMENT OF DIABETIC ACIDOSIS

The blood chemical determinations, fluid and insulin therapy, and response of urinary acetone and sugar, are shown for the first 16 hours after admission to the hospital. (J. R. E.—unpublished studies.)

by vein need not be the total replacement dosage, since after 100 milliequivalents equal to some 7.5 grams of potassium chloride, the patient can usually be started on an oral intake of foodstuffs which contain this ion. For detailed description of available solutions see table 24-III.

VI. Changes in Blood and Serum Solutes During Treatment of Diabetic Acidosis

The more or less characteristic electrolyte patterns present on the admission of acidosis and coma patients have been described earlier. Figures 15-5 through 15-7 show a series of patients, children as well as adults, in the early hours of treatment. It is to be noted that for purposes of showing recovery changes none of these patients received either lactate or potassium.

It can be readily seen that with therapy the bicarbonate rises slowly, while potassium and phosphate concentrations fall (figures 15-5, 15-6, and 15-7). Though not shown graphically, the sodium and chloride levels move

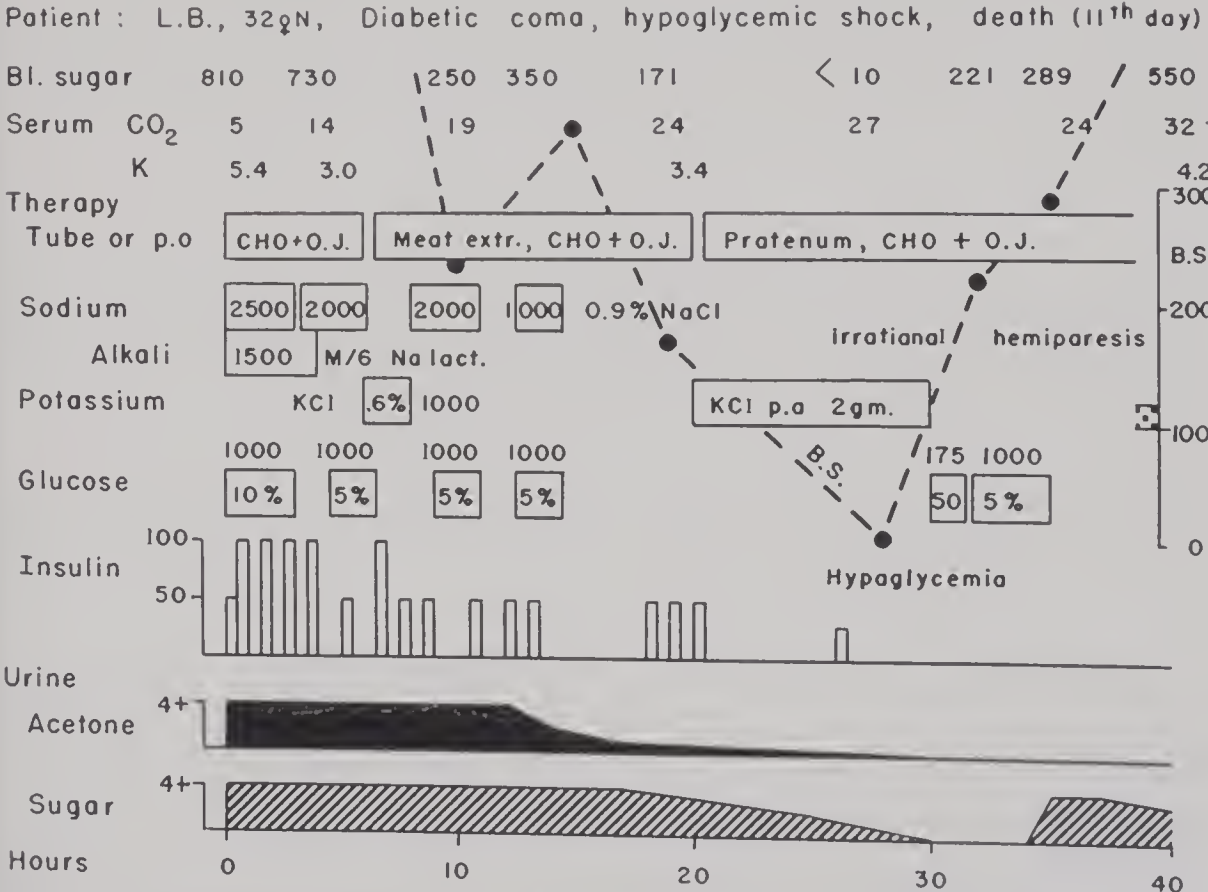


FIG. 15-10. TREATMENT OF DIABETIC ACIDOSIS COMPLICATED BY HYPOGLYCEMIA AND SUBSEQUENT DEATH

Inadequate intake of carbohydrate from the 15th to 28th hour resulted in hypoglycemic shock. Mental confusion and hemiparesis indicated central nervous system damage from which the patient never recovered. (Unpublished case study—J. R. E.)

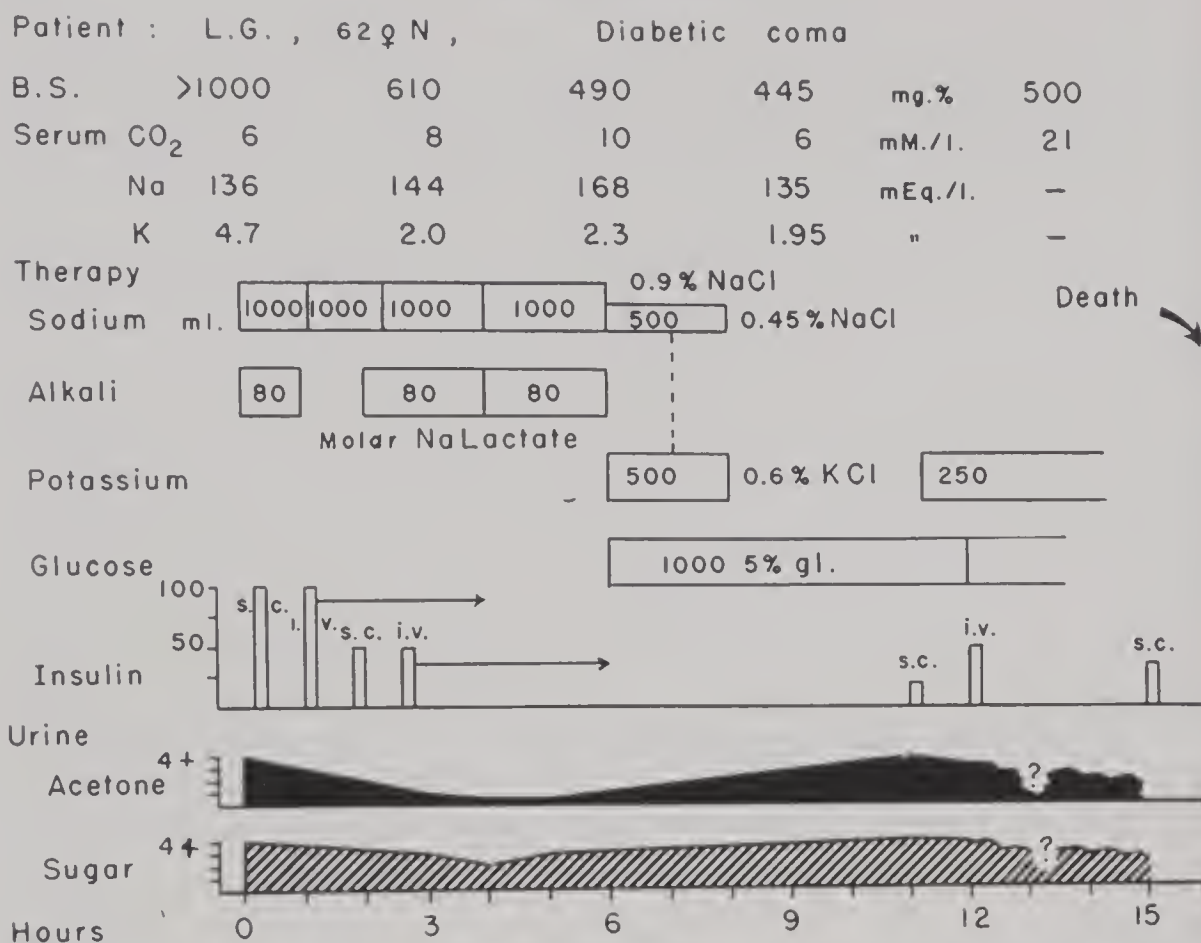


FIG. 15-11. TREATMENT OF DIABETIC ACIDOSIS COMPLICATED BY HYPOKALEMIA AND DEATH

Sudden respiratory failure at 16th hour may have been due to potassium deficiency; patient had received an unusually large amount of sodium ion (876 mEq.) and only 60 mEq. of potassium as KCl. Electrocardiographic tracings were characteristic of severe potassium deficiency (see next fig.). In addition insulin therapy from the 5th to 11th hour was inadequate. (Unpublished case study—J. R. E.)

upward to or above normal. The over-all responses are summarized in figures 15-8 to 15-12 as well as in an example in chapter 11 as figure 11-11.

## VII. Should Other Body Components Be Restored?

It is known that body stores of at least two other electrolytes, phosphorus and magnesium, become depleted in diabetic coma and it has repeatedly been noted, as shown above, that serum inorganic phosphorus falls markedly during the treatment (18a-d). Up to this point there is no evidence to indicate that this depletion produces untoward symptoms or that replacement via artificial solutions is beneficial. Hence, refuge is taken in the principle of "nothing harmful" and phosphate is given in the form of potassium salts while magnesium is withheld, since undue levels of the latter produce respiratory failure and labile hypotension (19).

It is probable that deficiencies of substances other than electrolytes and



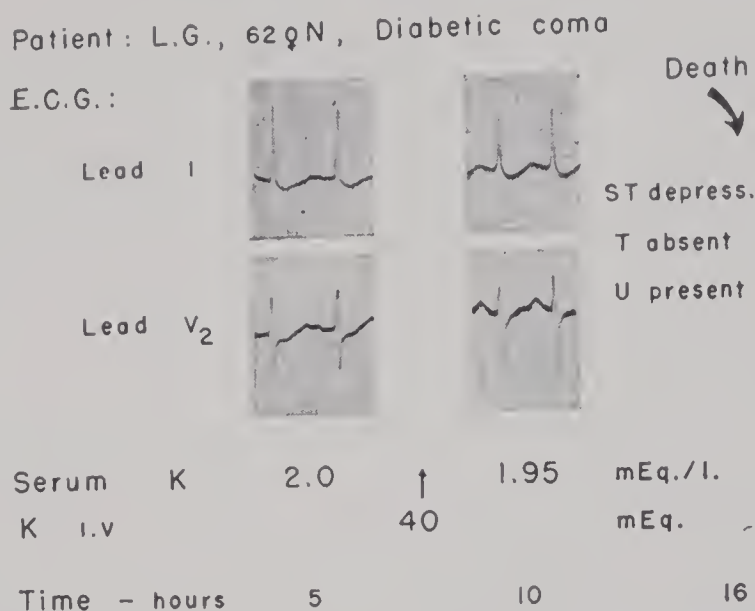


FIG. 15-12. ELECTROCARDIOGRAPHIC TRACINGS INDICATING SEVERE POTASSIUM DEFICIENCY IN DIABETIC ACIDOSIS

From the case illustrated in the preceding figure.

water develop during coma or therapy of coma, but as yet there is no evidence to justify the further complication of an already complex therapeutic program. The goal of choice should be the prompt restoration of intake to the point of a full diet as soon as it can be tolerated. This will permit cancellation of unidentified deficiencies.

**SUMMARY:** Diabetic ketosis and coma arise as a result of inadequate insulin secretion, failure to take insulin, increased food intake, decreased exercise, or infection. It is characterized by inadequate combustion of carbohydrate and increased protein and fat catabolism.

The diagnosis is based on a history of diabetes mellitus and the presence of confusion or coma, hyperventilation (Kussmaul breathing), ketonuria and/or ketonemia, glycosuria and hyperglycemia, low serum  $\text{CO}_2$  and buffer base, low blood pH, hypotension and tachycardia.

Fluid disturbances present in diabetic acidosis include sodium depletion, dehydration, peripheral vascular collapse, metabolic acidosis (loss of sodium plus increase in ketone acids), potassium deficit in cells and excess in extracellular fluid.

Therapy may be summarized as follows: insulin 100 units I.V. stat and repeat in 100 or 50 unit doses until ketosis abates, 0.9% NaCl, 2 to 4 liters, I.V. or S.C.; blood plasma or blood substitute for hypotension and incipient shock; 5 per cent glucose I.V. 1 to 3 liters 6th to 24th hour after insulin started (to help clear ketonuria and protect against hypoglycemia); 0.6 per cent KCl I.V. 1 liter after 6th hour if serum K concentration less than 3.0 mEq./liter, ECG indicates hypokalemia, or respiratory paralysis ensues.

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## Chapter 16

### FAMILIAL PERIODIC PARALYSIS

This rare disease entity is deserving of discussion because it illustrates the limited nature of our knowledge concerning potassium metabolism. Clinically it is characterized by episodes of weakness and inability to move the voluntary muscles with a diminished or absent response to galvanic and faradic stimulation. Rarely this is also accompanied by respiratory paralysis, presumably related to loss of motion of the diaphragm (1a-c).

As long ago as 1901 it was recognized that potassium salts were beneficial in the therapy of periodic paralysis (2a, b). The possibility that changes in the patient's own potassium stores might be related to or responsible for the paralytic episodes was first documented some two decades ago with reports that the serum levels of this ion were decreased during the attacks (3a-c). Subsequent studies have defined more precisely the events which result in hypokalemia. These have been facilitated by the fact that episodes of paralysis may be produced in such patients by the administration of glucose, insulin, or epinephrine, alone or in combination, and that they are known to follow a large intake of food (1c, 3b, c, 4a-c).

#### I. Origin of the Hypokalemia in Periodic Paralysis

##### A. *Minimal Role of Urinary Losses*

It has been observed that the "spontaneous" attacks tend to occur more frequently in the early morning hours (5). It is known of course that urinary losses of potassium continue during the postabsorptive period while the patient is asleep, though at a rate lower than that characteristic of the daytime period (6). It is possible therefore that this period of fasting and of potassium loss makes the patient more susceptible to a paralytic attack. However, the lowering of the serum potassium which has been observed to occur in most but not all instances of paralysis usually cannot be ascribed

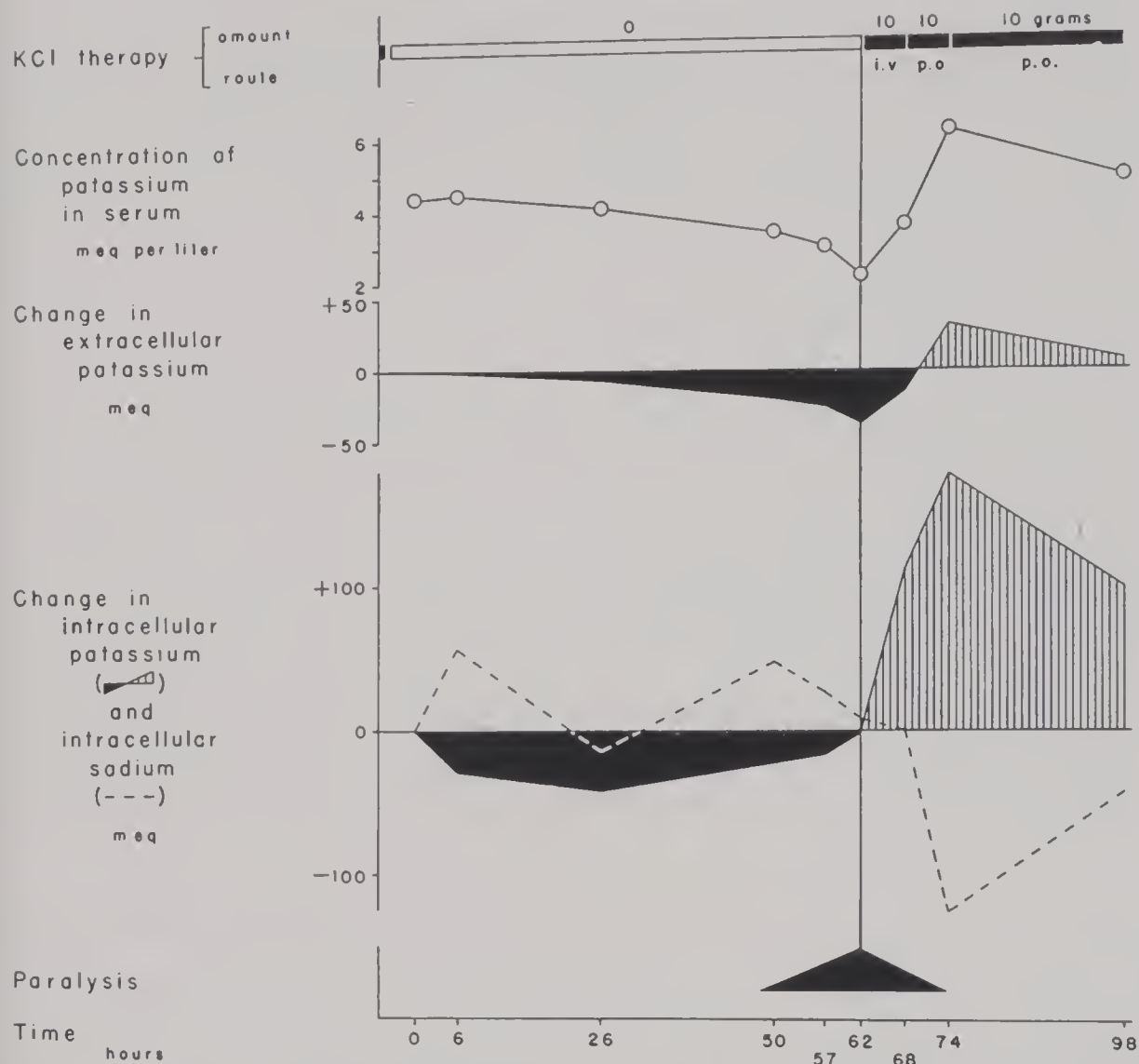


FIG. 16-1. CUMULATIVE EXCHANGES OF POTASSIUM DURING THE INDUCTION AND TREATMENT OF AN ATTACK OF PERIODIC PARALYSIS

Changes in extracellular potassium and intracellular potassium in excess of nitrogen are shown. The negative ones are solid black; the positive ones are lined vertically. The concentration of potassium in serum is plotted with open circles. The change in intracellular sodium is plotted with a broken line. The presence of paralysis is indicated by a solid black triangle at the bottom of the figure.

The data indicate that during the actual onset of paralysis, potassium moved from the extracellular to the intracellular phase. During treatment with KCl a positive balance of intracellular potassium was built up before the extracellular deficit was overcome. The change in cell sodium showed an inverse relationship to that of cell potassium. (From Danowski *et al.* (7a).)

to urinary losses of the ion. As a matter of fact, in the interval immediately preceding the seizure the urinary excretion of this electrolyte (fig. 16-1) may actually decline (7a, b).

In some of the reported studies, however, a significant urinary excretion of potassium did continue prior to and during the attack and undoubtedly



contributed to the net deficit of extracellular potassium. In one other patient an attack followed upon the ingestion of water which induced a diuresis and significant losses of potassium via this route (8). Despite this observation the hypokalemia still appears to result in great measure from transfers of extracellular potassium to other sites in the body, and presumably into cells.

### *B. Role of Transfers into Cells*

In the case of attacks induced by increased carbohydrate metabolism, such as that which follows insulin or carbohydrate administration, at least part of this transfer can be attributed to deposition of potassium in the liver during the formation of glycogen or to entry within cells during glycolysis. It has long been known that glycogenation and glycolysis involve such transfers of potassium (9a-c). On the other hand serial measurements of potassium levels during the disposal of glucose loads indicate that potassium may or may not decrease (9f). This contrasts with the much greater tendency for a drop to occur during insulin tolerances (9g) and points to a possible factor in the genesis of periodic paralysis. This could take the form of a transfer of potassium greater than normal occurring during the disposal of exogenous glucose or in response to insulin.

## **II. Relation of Serum Potassium Levels to Episodes of Paralysis**

A number of observations indicate that even though hypokalemia is a frequent concomitant of paralytic attacks in this disease entity, it need not be present or it may be quite minimal (10a-c). In addition it has been noted that comparable degrees of hypokalemia occur frequently in other disease states with muscle paralysis only rarely present (11a-d). Conversely, paralysis has been encountered in association with hyperkalemia (12a-b).

### *A. Redistribution or Ionization of Potassium in the Genesis of Paralysis*

The question then logically arises as to whether it is the gain of potassium by the cells rather than the loss of extracellular potassium that is responsible for the paralysis. However, it seems unlikely that the former *per se* produces the observed changes because temporary increases in cell potassium occur physiologically following ingestion or injection of this ion without producing the manifestations of this disorder (13a, b). It is possible that a combination of an extracellular lowering and an intracellular rise, (fig. 16-1) could sufficiently distort the cellular-extracellular ratio of potassium to interfere with the function of muscles, nerves, or synapses. Significant transfers of potassium are known to occur in conjunction with

stimulation, discharge, and recovery in all three of these sites (14). In addition to the clinically obvious disturbance of skeletal muscles, the attacks are characterized by changes in the electrocardiogram consisting of the so-called prolongation of the Q-T interval and a depression of the ST segment and the T wave. Such changes are also encountered in patients with low serum potassium of other causes (15a-c) (see fig. 15-12). The studies of Surawicz and Lepeschkin (15d) indicating that the QT change is often artefactual and related to the presence of a U wave, have already been mentioned in chapter 7. It should be pointed out that here too there is no constant level at which electrocardiographic changes invariably appear, and as a matter of fact they may be absent despite a pronounced hypokalemia.

Finally, if it is not the absolute level of extracellular potassium or the ratio of extracellular to cellular potassium that determines the onset of paralysis, perhaps it is the absolute amount of ionized cell potassium. The work of Jantz suggests this possibility, since in a large number of attacks he found that the ultrafiltrable potassium of tissues, but not of plasma, was reduced during attacks (16a-c). Our studies on the other hand indicated increases in osmotically active cell base (7a).

### III. Factors Other than Potassium in Periodic Paralysis

#### A. Creatinuria

It has been noted that creatinuria may be present between attacks of paralysis (17a). Ordinarily urinary creatine output is essentially zero in healthy adult males, whereas creatinuria appears in wasting diseases of muscles such as muscular dystrophy and in thyrotoxicosis (17b, c). It is of course regularly present in children and in healthy young adult women (17d, e). There are no clues as to the genesis of the creatinuria in these patients but its occurrence suggests that the muscles may be unable to accept all of the creatine provided to them for incorporation into creatine-phosphate complexes.

#### B. Hypophosphatemia

Several observers have reported that the induction of paralytic attacks by means of glucose or insulin also lowers the serum inorganic phosphorus values (18a). This is not surprising in view of the fact that increased carbohydrate metabolism following glucose or insulin invariably lowers the phosphorus levels in healthy subjects (9f, 18b). Hence such changes need not represent a specific defect in periodic paralysis and may be nothing more than the usual responses to these substances.

### *C. Possible Role of Other Electrolytes*

Finally, some statement is in order concerning the possible importance of conditioning factors in the production of clinical manifestations in this entity. It is known for example that hypokalemia suppresses hypocalcemic tetany (19a-d) and that calcium is an antidote for cardiac standstill produced by excessive levels of potassium (19e). In one of the studies (3b) it was noted that alkalosis, which alters the ionization of calcium, modified the characteristic pattern of attacks of paralysis. These fragmentary and unrelated data suggest that, though potassium plays a definite role in periodic paralysis, the entity cannot be explained solely in terms of our current knowledge of this ion. Studies suggesting that the injection of potassium during an attack relieved the seizure, even though the circulation of the involved extremities was segregated by means of tourniquets (17a), further complicate definition of this relationship. Failure to duplicate this effect in similar clinical experiments may or may not resolve this particular dilemma (7b, 20).

## **IV. Therapy**

The clinical manifestations of the disease disappear promptly following oral (one to eight grams) or injected (one to two grams) potassium chloride (fig. 16-1). This is usually true of the electrocardiographic changes but at times these may persist beyond the disappearance of the paralysis. Potassium chloride can be administered prophylactically, two to four grams each day.

**SUMMARY:** This relatively infrequent clinical disturbance of potassium metabolism illustrates that abrupt removal of extracellular potassium by transfers of this electrolyte into nonextracellular sites (usually without increased urinary excretion) can precipitate paralysis of striated musculature. Though such transfers occur spontaneously, they can also be induced by carbohydrate and insulin, alone or in combination. It is probable that in such circumstances the well-established deposition of potassium during glycogen formation and the entry of potassium into cells during glycolysis play a role. Unanswered questions point to limitations of our knowledge of potassium with respect to neural and muscular function: why do paralyzes also occur without decreases in serum potassium or with actual increases; does the ionization of cell potassium decrease during such attacks; do other electrolytes condition the appearance of weakness and paralyzes? Irrespective of the answers to these questions treatment is the same and consists of the prophylactic or therapeutic administration of potassium salts



*per os* or by vein in amounts sufficient to prevent or cancel paralytic attacks, i.e., one to several grams.

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## *Chapter 17*

### **WATER AND ELECTROLYTE CHANGES IN RELATION TO THE ANTERIOR PITUITARY, THYROID, GONADS, AND THE PAN- CREATIC ISLETS**

Experimental and clinical observations point to sodium, chloride, potassium and water effects related to the physiology or pathology of several of the endocrines. The roles of the anterior pituitary, the thyroid, the islets of Langerhans, and the gonads in such exchanges are discussed in this chapter. The well-documented electrolyte changes produced by altered adrenocortical activity are taken up separately in the chapter which follows.

#### **I. The Anterior Pituitary**

One-half of the cells of the adult anterior pituitary are thought to be non-endocrine. These have been named chromophobes because they stain poorly. Another 45 per cent of the cells are eosinophilic, while the remaining five per cent have basophilic properties (1a-c). The eosinophils and basophils elaborate proteins and polypeptides which in general can be said to influence, directly or indirectly, the metabolic activities of body tissues as a whole, and of certain organs or their products in particular, including the mammary glands, the thyroid, the adrenal cortex, the gonads, and the islets of Langerhans.

It should be pointed out that unanimity is lacking concerning the cell type which is the source of the particular trophic hormones of the anterior pituitary. Hence, the relationships which are presented in the sections which follow should be viewed as indicative of particular anterior pituitary effects without too much regard for the staining properties of the cells thought to be involved in the production of these hormones. However, in conformance with usual practice, the current views concerning the roles of the

pituitary cell types will be voiced as a frame of reference for the known interrelations.

#### *A. The Functions of the Eosinophil Cells*

The clinical observation that patients with giantism and acromegaly have adenomata of eosinophil cells suggests that these are the probable source of the growth factor which has been isolated from the anterior pituitary and which restores weight gain and development in immature hypophysectomized mice or rats (2a, b). Until very recently it has been impossible to separate this effect and an associated diabetogenic action of crystalline growth factor. Enough data are not as yet available to decide whether these two properties of growth hormone represent two separate chemical entities (3a-d). Hence, the view that the eosinophils also elaborate the diabetogenic factor is permissible. Finally, the opinion has been advanced that the eosinophils also give rise to thyroid-stimulating hormone and adrenocorticotrophin though most workers have attributed these functions to the basophils (4a, b).

#### *B. Water and Electrolyte Effects Possibly Attributable to the Eosinophil Cells*

The resumption of growth and development in hypophysectomized animals by means of growth factor isolated from the pituitary as well as its growth effects on the muscles and kidneys and the body fluid compartments of otherwise intact animals points to an influence upon the metabolism of foodstuffs and of minerals. The laying down of new tissue involves of necessity the incorporation of nitrogen, lipids, and sugars as well as potassium, phosphorus, and other electrolytes within cells and an expansion of other body fluid compartments. Hence, in this sense the growth factor can be stated to exert an influence on electrolyte and nitrogen metabolism (5a-g).

The only consistent change in serum or plasma electrolytes known to date to accompany growth hormone activity is a rise in serum inorganic phosphorus. This has been found to correlate with clinical evidences of a functioning eosinophil adenoma of the pituitary in acromegalic patients (6a, b) and may be the basis for the higher levels of inorganic phosphorus, discussed in chapter 6, in infants and in children when compared to full grown adults.

A number of observations however block acceptance of the view that growth is solely dependent on a specific hormone. Among these is the fact that in hypophysectomized mice a long-acting insulin will result in some resumption of weight gain, that in intact animals only transient changes in size and in composition of tissues are induced by growth factor, and that

in retarded children growth factor is usually without benefit (7a-f). Hence, at present it appears wisest to accept the fact that ablation of the anterior pituitary interferes with growth, but that the precise mechanisms in this disruption have not been identified.

The growth hormone-diabetogenic factor can produce diabetes mellitus by inducing a blockade of insulin at tissue levels in susceptible species and individuals (8a-c). Thereafter, the body fluid changes which accompany diabetic ketosis and coma can be elicited. There are no data concerning possible water or electrolyte concomitants, if any, of the known discharge of the alpha cells of the pancreas with a release of the hyperglycemic glyco-genolytic factor (glucagon) upon first exposure to growth hormone-diabetogenic factor (8d-f).

### *C. The Functions of the Basophilic Cells*

Studies of the histology of the pituitary during overactivity or underactivity of the various endocrines have led to the general belief that these cells elaborate the thyrotropic, adrenocorticotrophic, gonadotropic, lactogenic and possibly the melanophore factors (9a-h). Some workers have suggested on the basis of differential staining that certain of these functions are attributable to special groups of basophils (9i), but for all we know each cell may be capable of elaborating all of these hormones (9j) or as has already been pointed out the eosinophils may be the manufacturing site for some of these trophic hormones.

### *D. Electrolyte Effects of Basophil Cells*

It is obvious that increases or decreases in the hormonal output of the basophils will modify the activity of the target endocrine glands. The body fluid changes are therefore those which are associated with adrenocortical overactivity or underactivity as discussed in chapter 18, or those seen in hyperthyroidism or hypothyroidism, and in gonadal dysfunction as presented in Sections II and III of this chapter, respectively.

### *E. Effects of Total Destruction of the Anterior Pituitary*

Complete destruction of the anterior pituitary and loss of the trophic hormones as in Sheehan's syndrome or in Simmonds' disease or as a consequence of tumor or hypophysectomy produce characteristic changes in the target organs. The thyroid, adrenal, gonads, and mammary glands all diminish in size and function decreases (10a-c).

It should be pointed out however that in a series of destructive anterior pituitary lesions evidences of gonadotrophic and thyrotropic loss were more definite and appeared earlier than the signs of adrenocortical insufficiency (10d). This is in keeping with the fact that until recently very little thought



has been given to the possibility that destructive lesions of the anterior pituitary may alter electrolyte metabolism (10e-f). It has been generally assumed that destruction of the anterior pituitary by tumors has but little influence upon ion exchanges. This view has been abetted by the demonstration that the rodent and the dog can control sodium, chloride, potassium, and water excretion under nonstress conditions even in the absence of pituitary ACTH (10g, h). It appears probable that the human adrenal cortex also responds to variations in salt and potassium loads with appropriate adjustments in steroid output in the absence of the anterior lobe of the pituitary, since salt depletion and potassium accumulation of the classical Addison's disease type do not usually develop in Sheehan's syndrome, or Simmonds' disease, nor are they seen with expanding lesions within the sella turcica. There is evidence however that such patients do not respond to stress to the same degree nor as promptly as normals (10d). They therefore lack the usual margin of safety and ultimately actual adrenocortical insufficiency may appear.

If an antecedent diabetes insipidus is present in an experimental or clinical subject, its intensity is decreased with loss of the anterior pituitary. In the chapter dealing with diabetes insipidus it is pointed out that this amelioration merely reflects a decrease in solute load and that the inability to elaborate a concentrated urine persists.

If both the anterior and posterior pituitary are removed simultaneously, a transient diabetes insipidus of about one week's duration appears (10h). Thereafter, a persistent decrease in renal blood flow and in the clearance of test substances is demonstrable (10i-m).

## II. Thyroid

It is generally recognized that both hyperthyroidism and myxedema induce morphologic as well as functional changes in the other endocrines. Hence, in speaking of electrolyte and water changes in these two general disorders of the thyroid, it must be kept in mind that the end manifestation in each instance represents a combination of thyroid dysfunction and the resultant involvement of the adrenals, gonads, pituitary, etc.

### A. *Water and Electrolyte Changes with Thyroid Overactivity*

The increased energy exchange in thyroid overactivity understandably raises the insensible loss of water as well as the rates of water transfer through capillary membranes (11a, b). Irrespective of whether the hyperthyroidism originates intrinsically or in higher centers, body tissues are catabolized. Hence the percentage of body water increases. No definitive statement can be made concerning interstitial fluid, but plasma volume measurements by means of the dye or carbon monoxide methods show an

absolute increase (11c, d). With insufficient intake negative balances of nitrogen, phosphorus, potassium, and calcium are incurred. None of these changes produces any discernible alteration in the levels of serum or blood solutes, save for some lowering of the albumin levels (12a-c). The ionization of magnesium has however been reported to be decreased (13a-d).

### *B. Electrolyte and Water Changes with Hypothyroidism or Myxedema*

In hypothyroidism and particularly in myxedema the total body water and interstitial fluid are expanded both in percentage and in absolute terms while the plasma volume has been reported to be decreased (14a-c). This general excess of body fluids may be evident clinically even though the edema is of a nonpitting character. Its presence is however readily deduced from the diuresis which usually follows replacement therapy with desiccated thyroid. The fluid which is lost from the body during such diuresis contains large amounts of sodium, potassium and nitrogen (14d). The presence of the first two constituents suggests that both the interstitial and cellular compartments are expanded in myxedema. The high nitrogen content has been taken as an indication that protein is present in increased amounts in the interstitial fluid and that this fact accounts for the nonpitting character of the edema in myxedema. Actually this has not been established to be a fact and perhaps the turgidity of the tissues can be more rationally explained by cellular edema.

In myxedema serum protein levels are usually raised representing, in part at least, the decreased plasma volume (14e); other constituents may be somewhat abnormal. The variable degrees of change in the other solutes suggest that they are probably related to factors such as malnutrition. Finally, the binding of magnesium to proteins becomes altered so that all of this ion is readily ultrafiltrable (13a-d).

## **III. The Gonads**

In chapter 18 it is pointed out that estrogens and androgens which are adrenocortical type steroids are elaborated by the ovaries or testes as well as the adrenal cortices, and that these compounds can influence electrolyte exchanges and the intermediate metabolism of foodstuffs. Some of these effects are evident in events accompanying menstruation and in various virilizing syndromes; they can also be elicited by the administration of androgens and estrogens.

The body weight gain which accompanies the premenstrual molimen has been taken to be the result of an increased adrenocortical type steroid effect upon renal tubules, resulting in an undue retention of sodium (15a-c). There is no evidence that ovariectomy or menopause produces any change in the net sodium and water metabolism, nor should any be expected since

the adrenal cortex rather than the ovary is the chief source of the mineral regulating steroids.

Insofar as the adult male and female are concerned it is clear that the androgen-estrogen mixture determines in great measure the body build. Thus in the case of ovarian agenesis, adrenogenital syndrome, or a masculinizing tumor virilization occurs. This alters the body proportions of fat and water, increases the muscle mass, and in certain instances converts the serum carbon dioxide and chloride concentrations to the male pattern. Though the acute administration of androgens transiently lowers extracellular levels of potassium and phosphorus as nitrogen is deposited in cells, there is no evidence of a persistent change in these electrolytes in the masculinization syndrome (16a-d).

#### IV. The Islets of Langerhans

It has already been indicated that the electrolyte and water effects of glucagon or the hyperglycemic-glycogenolytic factor of the alpha cells, if any, have not been defined.

On the other hand the intravenous administration of insulin, the product of the beta cells which as usually prepared contains some alpha cell secretion, has long been known to produce a decrease in serum inorganic phosphorus and in potassium (17a-e). Recent studies in our laboratory indicate that other electrolytes may also change (17f). Thus 0.1 unit of insulin intravenously per kilogram of body weight induces marked electrolyte alterations in one-half hour or less. The potassium, serum inorganic phosphorus and bicarbonate levels all decline while chloride rises. These changes are in all probability indicative of ionic transfers between cells and extracellular fluid. Thus, it appears as if the entry of phosphate with glucose ultimately displaces cell chloride which in turn lowers the extracellular bicarbonate. The entry of potassium in this process could then be matched either by losses of cell sodium or by inactivation of cell base. On the other hand evidence is available indicating that if such administration of insulin results in glycogen deposition, then this process will by and of itself remove extracellular potassium (18a-c).

The water and electrolyte effects of diabetes mellitus which represents an absolute or relative deficiency of beta cell secretion have been discussed in chapter 15 which deals with acidosis and coma.

**SUMMARY:** The trophic hormones of the anterior pituitary can influence water and electrolyte metabolism either directly or through target organs. Thus, in the hypophysectomized preparation growth hormone permits resumption of growth and deposition of phosphorus, potassium, nitrogen and other cell constituents in the proportions in which they exist in health.



Higher than normal levels of serum inorganic phosphorus in the acromegalic provide a good index of excessive growth factor output by the eosinophil adenoma. The diabetogenic factor, closely associated with growth hormone in current separation procedures, blocks the peripheral action of insulin in certain animals and produces diabetes mellitus with its possible water and electrolyte changes. Thyroid-stimulating hormone elaborated in excess produces hyperthyroidism with the attendant increased exchanges of water and possible negative balances of nitrogen and cell electrolytes. Increased gonadal sex hormone output produces retention of nitrogen, phosphorus, potassium in addition to changes in body build and in secondary sex features. In the case of effects mediated through target endocrines, excesses of the products of these organs produce changes approximating those seen with trophic stimulation. This is true of the thyroid gland, the gonads, and the pancreatic islets.

Deficits of anterior pituitary secretions produce evidences of gonadotrophin lack before indices of thyroid-stimulating factor or ACTH deficiency appear. In these instances the water and electrolyte effects, if any, are those which accompany decreases or losses of the target glands themselves.

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"The leading and characteristic features of the morbid state to which I would direct attention are, anaemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of colour in the skin, occurring in connection with a diseased condition of the 'supra-renal capsules'."

Thomas Addison, 1868

## Chapter 18

### HYPO- AND HYPERFUNCTION OF THE ADRENAL CORTEX

The clinician's view concerning the role of the adrenal cortex in health and in disease has changed. Until several years ago the all or nothing attitude generally prevailed, i.e., either the patient had classical Addison's disease or the adrenal cortex was perfectly normal. The fact is that various gradations of hypo- or hyperadrenocorticism may be encountered, and that aspects of adrenocortical activity other than control of salt and water exchanges may be involved in these states.

#### I. General Physiology of the Adrenal Cortex

As a mnemonic device it is useful to look upon the adrenal cortex as a tripartite organ, even though from the functional view such clear-cut separation may not be the fact (1).

##### *A. The Inorganic or Mineral-Regulating Effects*

Results of studies with rats based on salt-loading or salt deprivation (2a-c) suggest the schematic view that the outermost layer or *zona glomerulosa* can be considered to be the chief source of a steroid, or steroids, which facilitates the reabsorption of sodium from the glomerular filtrate, enhances the urinary excretion of potassium, and influences the excretion of water (2d, e). Control of this aspect of renal function is thought to be mediated via steroids for which the synthetic compound desoxycorticosterone or DOC has been cited as a prototype (2f-i). There is now satisfactory evidence that the adrenal cortex does contain and elaborate DOC (2j, k) but it is not, as we shall see, the sole mineral-regulating steroid. Furthermore, evidence is available indicating that factors other than the adrenal cortices can influence electrolyte metabolism in the absence of these glands (21).

In 1953 Reichstein announced the isolation of a crystalline steroid from

the amorphous fraction of the adrenal cortex. Surprisingly enough, though this compound differs from DOC in having an oxygen in the 11 position, it is some 25 or more times as potent as DOC in altering electrolyte excretion (3a-c). It has been named aldosterone or electrocortin; its chemical structure is shown in figure 5-3. This is presumed to be the hormone of the adrenal cortex which is predominantly concerned with electrolyte and water changes. Its role in the intermediate metabolism of foodstuffs or in other physiologic or biochemical processes is yet to be determined, though a glycogenic effect has already been reported (3d).

The administration of DOC, Compound E, or ACTH to animals or to human subjects without restriction of salt intake produces retention of sodium, chloride, and water, losses of potassium, and a gain in body weight. Serum levels of chloride fall, total  $\text{CO}_2$  content rises, and hypokalemia appears as deficits of cell potassium develop. Cell sodium increases (3e-j). If cortisone or ACTH is given during sodium restriction a definite increase in extracellular volume and in extracellular sodium and chloride still appears (31). This must be the result of transfers of water, sodium and chloride from cells since body weight does not change and external transfers are virtually nil. This effect is transient however and disappears with continued therapy, in contrast to the persistence of the changes when sodium is not restricted.

The incidence and the persistence of the hypochloremic metabolic alkalosis described above do not appear to be decreased or eliminated by marked sodium restriction together with a daily potassium intake of 150 milliequivalents or more (3h).

In patients ACTH or cortisone produces variable increases in glomerular filtration rate and in renal blood flow with definite evidence of increased tubular reabsorption of water (3e, f, m, n). It should be pointed out however that the observed effects may not be the results of a direct renal action (3o). The increased reabsorption of sodium and diminished excretion of potassium which are the predominant mineral effects of these agents on the renal tubule are also demonstrable in the gastrointestinal tract in hypo- and hyperadrenocorticism with the aid of resins (see sections II and V of this chapter).

### B. The Organic or Oxysteroid Effects

The intermediate layer or *zona fasciculata* is believed to elaborate the bulk of the 11-oxygenated steroids. Compound E or cortisone (17-hydroxy-11-dehydrocorticosterone) and Compound F or hydrocortisone (17-hydroxy-corticosterone) serve as prototypes of this class of steroids. The former is a laboratory product while the latter is thought to be the chief 11-oxygenated steroid elaborated by the adrenal cortex of animals and

TABLE 18-I. EFFECTS OF ADRENOCORTICAL STEROIDS WHEN GIVEN IN APPROPRIATE DOSAGE

EFFECTS OF ADRENOCORTICAL STEROIDS WHEN GIVEN IN APPROPRIATE DOSAGE		
	BIOCHEMICAL EFFECT	CLINICAL EFFECT
A. INORGANIC OR MINERAL REGULATING EFFECTS OF THE MINERALO CORTICOIDS: Electrocortin, DOC, Cpd E, F, Androgens	Incr. tubular reabsorption of Na, Cl, H <sub>2</sub> O Incr. urinary excretion of K Hypochloremia, alkalosis Hypernatremia, hypokalemia	Edema Hypertension
B. ORGANIC OR OXYSTEROID EFFECTS OF THE SUGAR-FAT-NITROGEN HORMONES OR GLYCOCORTICOIDS: Cpd E, F, Electrocortin, Androgens, DOC	Incr. gluconeogenesis Incr. resistance to insulin Incr. liver glycogen Anti-anabolic Mobilization of fat	Transient Diabetes mellitus  Transient Neg. N. bal. Changes in body contour  Eosin. decr., PMN incr., Lymphs. decr., RBC incr., Baso. decr.  Anti-inflammatory  Anti-hypersensitivity
C. ANDROGENIC EFFECTS: Androgens, Cpd E, F, DOC = zero, ? Electrocortin*	Anti-hyaluronidase or Anti-spreading factor  Decr. complement Decr. antibody production Anti-hyaluronidase  Retention of N, K, Phos. ? other effects	Facial hirsuties Decr. voice pitch, Acne Amenorrhea Masculine body build

\* In order of diminishing intensity



humans. These compounds affect electrolyte and water excretion in a manner similar to DOC or electrocortin, but they are less potent. Thus cortisone, milligram for milligram, is about  $\frac{1}{25}$  as effective as DOC in this regard (4a, b). These and other biochemical and clinical effects of 11-oxysteroids when administered in pharmacologic dosage are listed in table 18-I.

The chief influence of the 11-oxysteroids is exerted upon the intermediate metabolism of foodstuffs, upon circulating formed elements of the blood and fixed lymphoid tissue, and finally upon membrane permeability. The evidence for the first of these consists of the demonstration that pharmacologic doses of compound E or F alter carbohydrate metabolism (increased gluconeogenesis, diminished peripheral utilization of glucose, increased glycogen formation, and increased insulin tolerance), interfere with protein anabolism (negative nitrogen balances), and augment the catabolism of fat (respiratory quotient changes) (5a-c). This is illustrated in figure 18-1. It should be emphasized that some of these responses can be modified or even reversed by dietary alterations. Thus, high protein intake will cancel the negative balances of nitrogen.

The effects on blood cells and lymphoid tissue include decreases in lymphocytes in the circulation and in the lymph nodes, a diminution of circulating eosinophils and perhaps basophils and an increase, both relative and absolute, in the polymorphonuclear granulocytic cells (6a-d).

The evidence that membrane permeability can be modified consists of the demonstration that dyes leave the synovial space at a greater rate, that inflammatory processes subside, and that transfers of electrolytes in renal tubules and other tissues are altered (7a-g).

### C. The Androgenic and Anabolic Effects

The innermost sphere of the cortex, *zona reticularis*, is presumed to elaborate androgenic compounds with virilizing and protein anabolic properties. Potassium and phosphate are retained during periods of positive nitrogen balance (8a-c). In the male the output of these compounds from the adrenal cortex is supplemented by the interstitial cells of the testes. Steroids of this class from either of these sites appear in the urine in the 17-keto form.

Despite this breakdown of the adrenal cortex on an anatomical and functional basis it should be kept in mind that the properties of the individual steroids are best viewed as a spectrum. Thus, the androgenic-anabolic steroids as well as the oxysteroids can induce retention of the chief extracellular electrolytes and losses of potassium, even though the endogenous adrenocortical products most effective in this respect are the mineral-regulating steroids. Similarly, though the intermediate metabolism of carbohydrate, fat, and protein is most markedly influenced by the oxysteroids

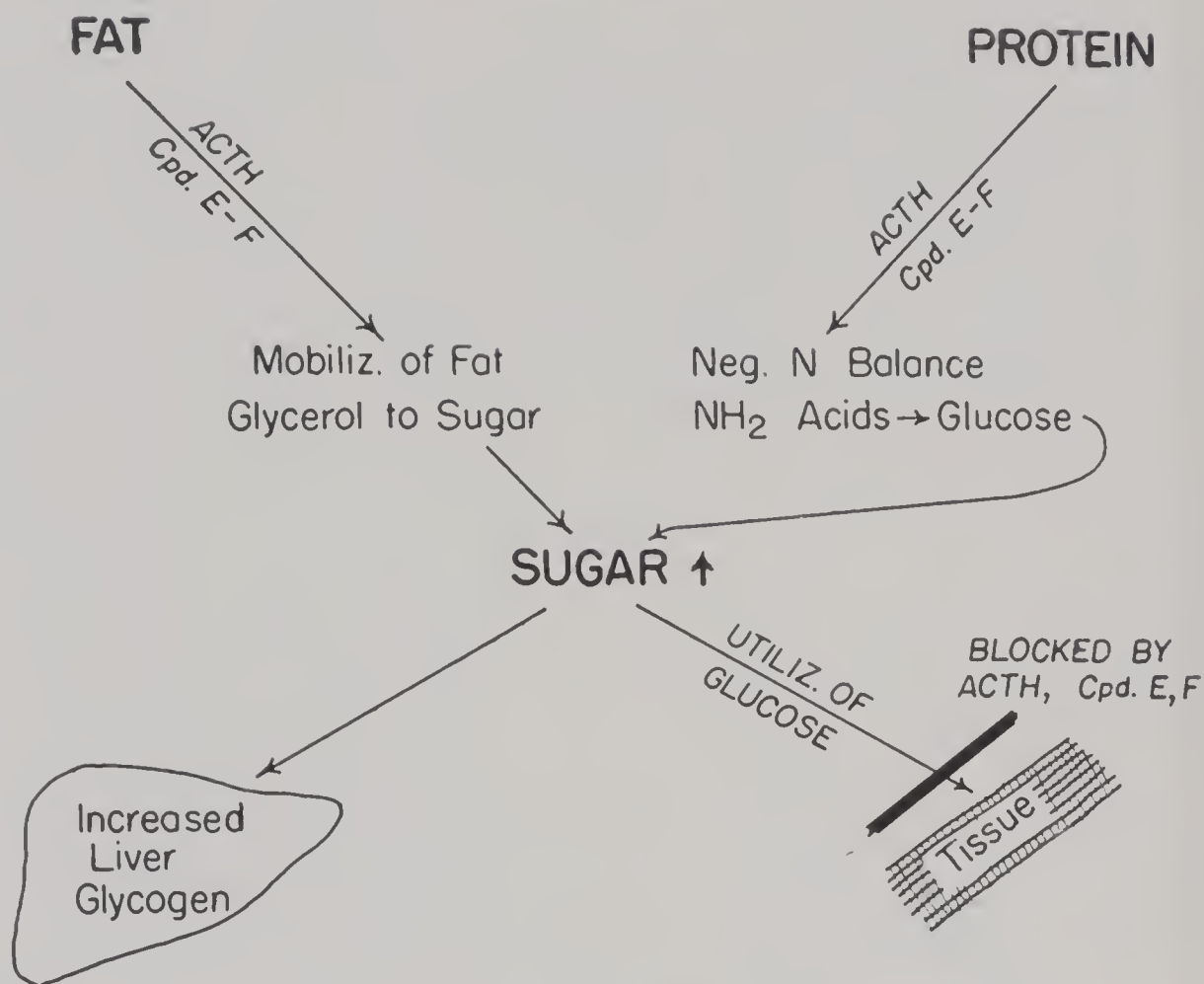


FIG. 18-1. CARBOHYDRATE EFFECTS OF OXYSTEROIDS

Oxysteroids increase gluconeogenesis from amino acids and from fats and at the same time block the peripheral utilization of glucose. The extra carbohydrate supplies facilitate the deposition of glycogen. This effect has been used in adrenalectomized animals as an assay technique for oxysteroids.

and the androgenic-anabolic hormones, the 11-desoxy mineral-regulator, DOC, is not totally devoid of these effects (9a-d). An attempt to quantify the gradation of the biological and biochemical actions of the mineral-regulating, the so-called sugar-fat-protein hormones and the androgenic-anabolic steroids is presented in table 18-I. It should also be pointed out that under some circumstances the activities of the individual steroids are not necessarily additive and, as a matter of fact, may be antithetical (9e-h).

## II. States of Adrenocortical Hypofunction

Loss of normal adrenocortical function or responsiveness can occur as a consequence of destruction of these glands by tuberculosis, fibrosis of unknown origin, or hemorrhage as in the Waterhouse-Friderichsen syndrome (10a-c). On the other hand profound functional depression can be produced by the administration of cortisone, hydrocortisone, and probably by other steroids as well (11a-c) and is present in varying degrees in anterior pituitary

insufficiency which results in a decrease or a total loss of the trophic hormone to the adrenal cortex. Whether the latter state can be brought on even in transient form by ACTH administration has not been answered though some compatible data are available (12a, b). Finally, it may occur as an exhaustion phase following prolonged stimulation (13a-d).

#### A. Addison's Disease: Metabolic and Clinical Manifestations

In classic Addison's disease there is a complete loss of adrenocortical function though some adrenocortical type steroids, as evidenced by continued though reduced 17-ketosteroid excretion, are still produced in small amounts by the gonads (14). With the absence of sufficient quantities of the salt-regulating steroids, potassium excretion falls off and this ion accumulates inside cells and in the extracellular fluid (15a-f). Simultaneously, the reabsorption of filtered sodium and chloride in the renal tubules becomes inadequate. The excretion of water loads falls off, i.e., the Robinson-Power-Kepler test becomes positive (15g). These changes are shown in figure 18-2. The salt content of sweat rises and there is evidence, based upon the demonstration that cation exchange resins remove much greater amounts

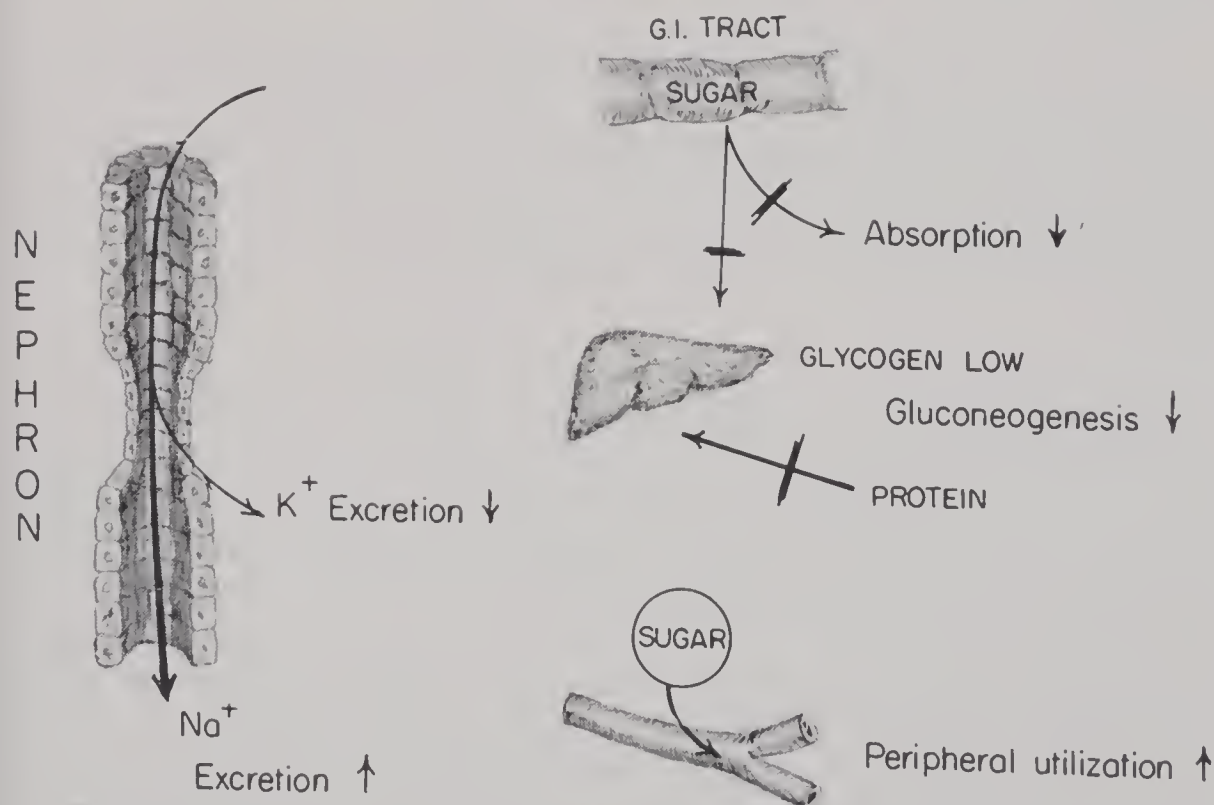


FIG. 18-2. MINERAL AND CARBOHYDRATE CHANGES IN ADDISON'S DISEASE

Adrenocortical insufficiency decreases the reabsorption of sodium from glomerular filtrate and interferes with the renal excretion of potassium. In current views this represents an interference with the cation exchange processes whereby sodium re-enters the body fluids in an exchange which involves the passage of either potassium or hydrogen into the tubular lumen.



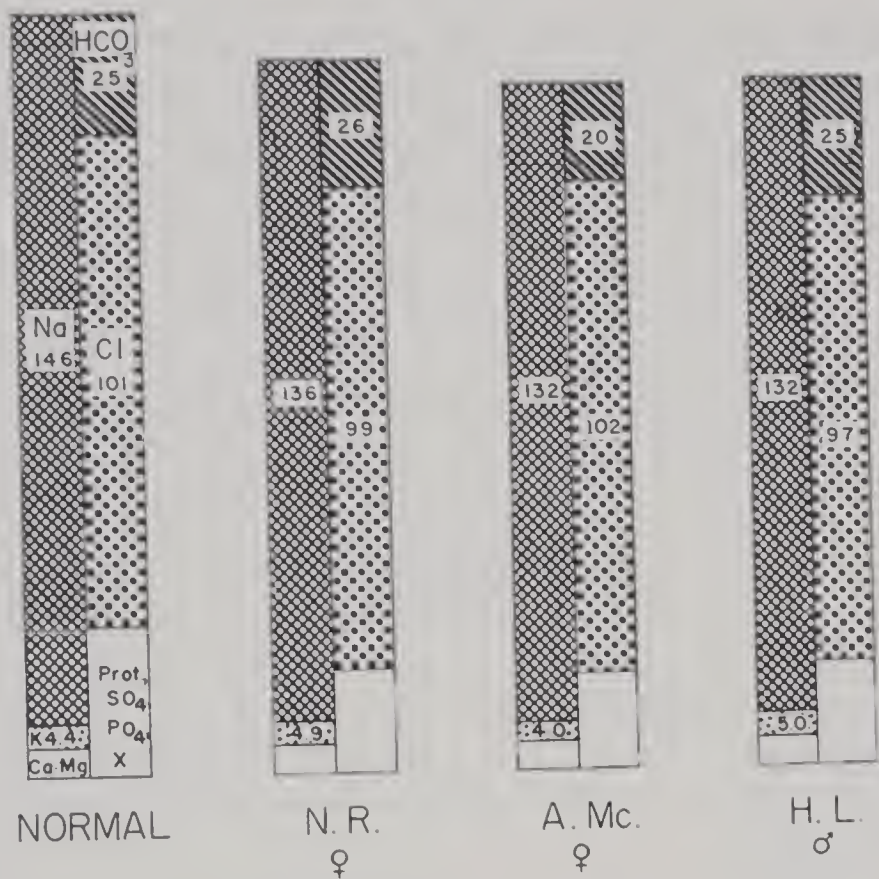


FIG. 18-3. ELECTROLYTE CHANGES IN UNTREATED ADDISON'S DISEASE  
N. R., a 65-year-old female (B); A. Mc., a 39-year-old female (C); H. L., a 38-year-old male (D). Mean normal values are shown in (A). It is to be noted that despite the presence of adrenocortical insufficiency of the chronic type, the only electrolyte change is a moderate hyponatremia. Potassium was not elevated in these cases nor was the level of bicarbonate and chloride regularly depressed, though all these changes can develop. (Danowski *et al.*, unpublished data.)

of sodium, indicating that the impetus for absorption or reabsorption of sodium from the gut is diminished (15h-i). Whether or not deficits of sodium, chloride and water develop depends upon the concomitant intake of salt (figs. 18-3 and 18-4). If the latter covers or more than covers all losses, salt and water stores remain intact. If not, then deficits develop. As salt depletion progresses, extracellular and plasma volumes decline and circulatory collapse ensues (15j-o).

With the absence of adequate amounts of 11-oxysteroids the intermediate metabolism of foodstuffs is altered. At the same time the new formation of glucose from amino acids is decreased and the blocking effect of the steroids upon insulin action at tissue and cell levels is absent. Liver glycogen stores decrease. All of these changes, related predominantly to the 11-oxysteroid deficit, tend to produce hypoglycemia (15p). These effects of changes in intermediate metabolism are accentuated by inadequate gastrointestinal absorption of sugars, and presumably of fat and protein products, as a con-

sequence of the circulatory collapse. These changes are shown in figure 18-2. Other reflections of decreased 11-oxysteroids may also be present in the form of eosinophilia and lymphocytosis.

The lack of the protein-anabolic androgenic steroids contributes at least in part to the weight loss and weakness. In addition decreased libido and amenorrhea may develop (15q).

The pigmentation and freckling which develop represent the effects of increased amounts of pituitary melanophore factor which is associated with the increase in ACTH characteristically present in most instances of Addison's disease (15r-u).

Acute crises characterized by circulatory collapse and hypoglycemia of sufficient severity to produce death may develop with otherwise minor infections. The crisis is usually ushered in by nausea or vomiting which should therefore be received as an ominous sign.

### *B. Therapy of Addison's Disease in Nonacute and Acute Phases*

Treatment of the nonacute Addisonian patient includes DOC pellet implantation every nine to 12 months, usually three in number, each weighing approximately 125 mg., and daily oral cortisone, 25 mg. On this regimen an ordinary salt intake is both permissible and adequate and there is neither a need nor is it desirable to restrict potassium (16a-i).

In treating an Addisonian crisis therapy should include plasma or colloid as well as salt and water to correct the circulatory collapse and glucose to remedy the hypoglycemia. At the same time adrenocortical extract, up to 400 to 500 cc. a day, cortisone 500 to 1000 mg., and DOC 5 to 10 mg. should be given. Alternatively, hydrocortisone may be administered (100 mg. i.v. plus 100 mg. i.m.).

## **III. Adrenocortical Hypofunction following Cortisone Therapy**

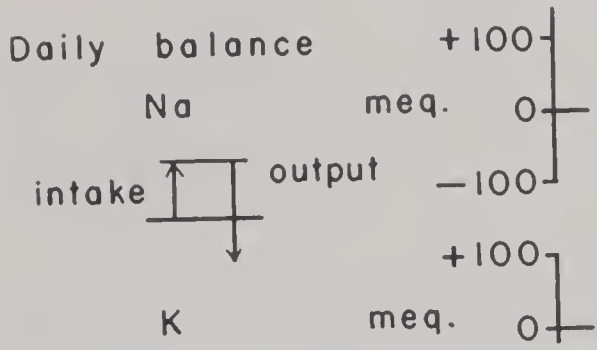
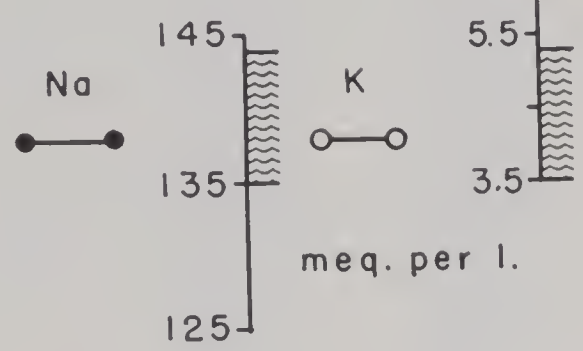
The administration of cortisone to patients with grossly normal adrenal cortices promptly depresses the output of steroids. This response is analogous to the effects of feeding thyroid to a normal individual (17a-c). Withdrawal of the cortisone is followed by a period of adrenocortical hypofunction or relative unresponsiveness to physiologic stimuli. This may last many weeks or months and represents a hazard in case of accident, infection, or surgical intervention (11a-c, 18a).

Treatment is based on an awareness of this hazard. It seems reasonable to accompany or to follow the cortisone with a period of ACTH therapy or to try very gradual withdrawal of the cortisone (18b). In the post-treatment phase the patient and his physicians should be aware of the hazard and any event which may represent a physiologic burden must be met with cortisone supplementation.

Patient T. S.  
Diagnosis Addison's Disease

Therapy

Serum conc.



Day of study

Interpretation of serum concentrations

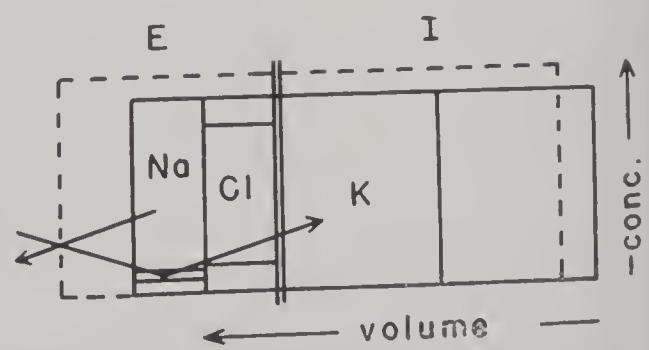
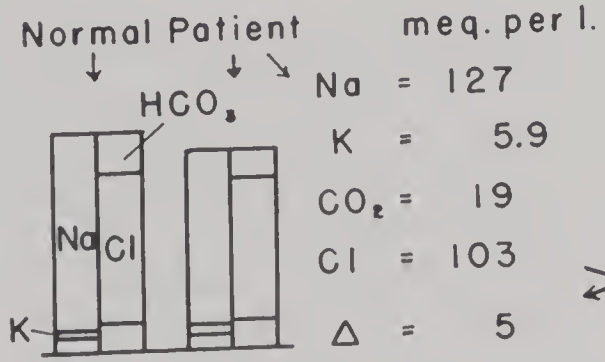


FIG. 18-4. BODY FLUID CHANGES IN ADDISON'S DISEASE. SERUM CONCENTRATION: LOW SODIUM, HIGH POTASSIUM

Clinical data and diagnosis. T. S., a 50-year-old Negro male with weakness, hypotension and increased pigmentation, had a negative sodium balance and hyponatremia on salt restriction, as well as a positive potassium balance and hyperkalemia, while the volume of urine was normal. Diagnosis of adrenocortical insufficiency (Ad-



#### IV. Combined Hypo- and Hyperfunction of the Adrenal Cortex

An entity characterized by salt-wasting, though not regularly, and either precocious sexual development or masculinization occurs in children and adults. This has been called the adrenogenital syndrome. From the functional viewpoint it represents a combination of a variable underproduction of salt-regulating and 11-oxysteroid compounds and an overproduction of androgenic steroids (19a-f). Continued therapy with small amounts of cortisone, 15 to 50 mg. each day, corrects both of these abnormalities, returning the 17-ketosteroid output to normal and stopping progression of the sexual precocity or masculinization. It has been suggested that the cortisone suppresses the abnormal adrenocortical activity either directly or via ACTH (20a-d).

#### V. Excesses of Adrenocortical Type Steroids

A variety of causes may result in an excess of adrenocortical steroids. These include adrenocortical hyperplasia and tumors, as well as the continued administration of ACTH, cortisone, DOC, Cpd F, or androgens in excess of actual replacement needs. An excess of adrenocortical type steroids will produce to a greater or lesser degree the changes listed in table 18-I as pharmacologic effects. The clinical and biochemical manifestations will depend upon the particular steroid or steroids which are present in excess.

##### A. Tumors or Hyperplasia of the Adrenal Cortex

Functioning tumors of the adrenal cortex or hyperplasia usually result in a Cushing's syndrome. In this entity there is evidence of disturbances in electrolyte and water excretion in that alkalosis and hypochloremia usually develop and the serum potassium level falls. On the other hand sodium retention and edema are not prominent features of this syndrome and, as a matter of fact may not be present at all. The blood pressure may or may not be elevated.

The intermediate metabolism of foodstuffs is altered in that insulin resistance develops. Actual diabetes mellitus occurs with increased frequency

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dison's disease) was thus confirmed. He responded well to therapy with desoxycorticosterone.

Interpretation of serum concentration at end of day three: *Body fluid pattern:* Deficit of salt in relation to water with contraction of volume of extracellular phase (E) and expansion of volume of intracellular phase (I). Potassium retained in both phases.

*Physiologic mechanisms:* Adrenocortical insufficiency caused decreased renal tubular reabsorption of sodium and decreased excretion of potassium. Low concentration of sodium in extracellular fluid and possibly increased concentration of potassium in intracellular fluid caused shift of water from extracellular to intracellular phase. (From Squires and Elkinton (15h).)

in these patients, but this is obviously not directly related to the excess of steroids, since diabetes is not an invariable finding. There is no evidence that the net exchanges of protein are changed in these patients. On the other hand redistribution or new deposit of body fat does occur in view of the moon face, buffalo hump, abdominal pad and striae, and the spindly legs and arms which develop.

In addition to the altered body contour, patients with Cushing's syndrome often have evidences of increased androgenic activity characterized by masculinization of females as manifested by a lowering of the voice and increase in facial hair. Acne may appear. Amenorrhea usually develops. The urinary output of 17-ketosteroids rises (21a-f).

**1. Differential Diagnosis of Hyperplasia, Benign Adenoma and Cancer of the Adrenal Cortex.** All three of these diseases can produce the same clinical changes (21f, 22a). Two procedures, the 17-ketosteroid output and the response to cortisone, are often of assistance in the differential diagnosis. When the ketosteroid output is very high, i.e., 100 or 200 mg. in 24 hours, a cancer is highly probable. Lower values, such as 25 or 50 mg. per day, values which are still above the usual range for the patient's age and sex, favor adenoma or hyperplasia (22b-h). The administration of cortisone in the latter two groups will return the 17-ketosteroid excretion to the normal range but will not affect the very high output occurring in cancer.

Treatment of one of these forms of Cushing's syndrome or hyperadrenocorticism consists of adrenal exploration and removal of hyperfunctioning tissues; benefit has also been reported following pituitary irradiation. It is also possible that ultimately the use of compounds such as DDD, 2,2-bis-(parachlorophenyl)-1,1 dichloroethane, an agent which destroys the *zona fasciculata*, will be feasible for this purpose (22i-k).

#### *B. Effects of DOC, Cortisone, ACTH, or Androgens in Excess*

In contrast to the relative infrequency of edema in Cushing's syndrome, patients with DOC intoxication, i.e., those with Addison's disease on pellet therapy in excess of their needs, very quickly develop sodium, chloride, and water retention as well as hypertension. This is accompanied by potassium depletion as well as a rise in the total carbon dioxide content of serum not prevented by the withholding of sodium. There are no evidences of carbohydrate disturbances nor does masculinization occur. Eosinophils are usually not decreased. In the experimental animal DOC administration with restriction of potassium results in necrosis of the myocardial and skeletal musculature (23a-f).

Patients receiving cortisone or ACTH with insufficient restriction of

sodium intake develop edema as quickly as those with DOC excess, even though the latter has a more pronounced effect on mineral excretion. However the lesser potency of cortisone or ACTH in this regard is made up by the larger dosages employed. There is some suggestion that ACTH may be less apt to produce the inorganic or mineral changes than is cortisone (24a-d). In the patients treated with ACTH one of course still finds the other evidences of 11-oxysteroid overactivity mentioned earlier: thus insulin tolerance rises, the body contour changes, and androgenic effects appear. With ACTH, but not with cortisone, freckling and pigmentation of the type seen in Addison's disease also develop.

With excessive androgen administration the masculinizing effects (hirsutism, etc.) are promptly evoked, and with the passage of time retention of sodium, chloride, and water also occur. These compounds have, as has been mentioned earlier, a protein anabolic effect which leads, at least in the earlier phases, to nitrogen and potassium retention.

### *C. Prevention or Cancellation of Toxic or Side Effects of ACTH or Cortisone Therapy*

The onset of edema frequently necessitates withdrawal of ACTH and cortisone therapy, though some of the other biochemical abnormalities such as hypokalemia, alkalosis, hyponatremia may also be construed as contraindications to continued maintenance on these drugs. It is obvious that limiting the dosage and the duration of therapy will deprive patients of improvement that might be otherwise elicited.

A number of approaches to a resolution of this problem have been suggested aside from ammonium chloride and mercurial diuresis. Cation exchange resins have been tested for this purpose (25). These agents produce hyperchloremia and acidosis, abstract sodium, and, when given in the appropriate cycle or form, result in potassium retention. All of these are desirable properties since they are the antithesis of the biochemical effects produced by cortisone or ACTH. Unfortunately their limited efficiency does not eliminate the need for considerable dietary restriction of salt, even though potassium depletion can be prevented and hyperchloremia and acidosis minimized (25). Rigid restriction of dietary sodium has by itself proved quite adequate in preventing sodium retention and edema in patients receiving cortisone or ACTH in large amounts, up to 300 mg. per day, for many weeks (26a, b). These diets have been described in chapter 9 and samples are included in the appendix tables. Their high potassium content prevents depletion of this electrolyte. Though some hyponatremia and alkalosis do occur, they appear to be of lesser intensity. Other side effects such as moon facies and acne are not modified by this regimen. Finally, a high potassium intake minimizes sodium retention which otherwise occurs



on general diets (27a-c). Obviously, in patients with underlying renal disease and a tendency to potassium accumulation neither the low sodium-high potassium regimen nor the administration of potassium salts is feasible.

**SUMMARY:** From the functional view it is helpful to consider the adrenal cortices as elaborating steroids which exert three principal groups of effects: a) regulation of electrolyte and water output, i.e., increasing sodium and chloride reabsorption and facilitating potassium and water output, b) modification of the intermediate metabolism of foodstuffs, i.e., at least on initial administration, producing negative balances of nitrogen, mobilizing fat, increasing gluconeogenesis, interfering with the peripheral action of insulin and facilitating glycogen deposition, and c) production of androgenic effects or masculinization as reflected in body build, voice pitch, and secondary sex features. In the past the first group of effects was attributed to the 11-desoxysteroids and the second group to the 11-oxysteroids, but the advent of aldosterone or electrocortin, an 11-oxy compound with marked sodium retaining effects makes this classification untenable; the androgenic effects are attributable to steroids elaborated by adrenal cortices as well as by testes.

With complete loss of adrenocortical steroids Addison's disease develops with sodium depletion and potassium retention as a result of inadequate reabsorption and excretion of these two ions respectively, hypoglycemia by virtue of slower gastrointestinal absorption, decreased gluconeogenesis, removal of the steroid blockade of insulin action, liver deglycogenation, and finally, losses of libido and muscle strength as a consequence of androgen deficits.

Excesses of adrenocortical steroids in general produce sodium retention and potassium deficits, the latter accompanied by hypochloremic alkalosis; diabetes mellitus may appear in susceptible individuals together with secondary sex changes.

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## Chapter 19

### DIABETES INSIPIDUS AND OTHER DISORDERS OF THE ANTIDIURETIC SYSTEM

In previous chapters it has been pointed out that there are cells within the hypothalamus which are sensitive to changes in the concentrations of the solutes within the extracellular fluid. These osmoreceptors of Verney bring about an increase or decrease in the output of humoral anti-diuretic materials by the posterior pituitary which in turn lowers or raises, respectively, the renal output of water (1a-c). By virtue of this mechanism excesses of water which lower the extracellular solute concentrations are excreted as dilute urine, whereas deficits of water lead to conservation of the remaining body water by restricting urine volume to a minimum. It has been shown however that large solute loads during dehydration will interfere with this conservation mechanism (2a-d) and conversely that coitus, emotional disturbances, drugs such as morphine, and colloids in hyperoncotic concentrations can inhibit water diuresis (3a-h).

Until the advent of more precise technics and studies it has been generally assumed that the posterior pituitary is the sole site for the production and storage of the antidiuretic substance or substances. At present it is clear that these humoral agents are present in the body fluids even after hypophysectomy, though in reduced amounts, and that under such circumstances the hypothalamus is at least one of their sources (4).

It is obvious that facts obtained by means of these newer methods may necessitate a revision of current views of how this and related mechanisms operate in regulating body fluids in health and how disruptions occur in disease states such as diabetes insipidus, anterior pituitary insufficiency, intractable edema, and particular types of cerebral injury.

#### I. Diabetes Insipidus

##### A. *Etiology*

Injury to the hypothalamus, to the hypothalamic-hypophyseal tract, or to the posterior pituitary can result in diabetes insipidus (5a). An intra-

cranial tumor is the most frequent known cause of the syndrome, but in an even larger number, as in 50 of Blottner's 112 cases, the origin of the disease cannot be identified (5a-c). Included in this latter group are the hysterical patients in whom a large fluid intake induces polyuria. These can be differentiated, though with some difficulty, from the patients with organic lesions in that they respond to fluid restriction by an increase in specific gravity of the urine (5d). Both groups of patients, i.e., those with an organic lesion and those with a psychic disturbance, decrease the urine output, raise its concentration, and lower the water intake in response to pitressin, the antidiuretic factor isolatable from the posterior pituitary. Only diabetes insipidus due to defective production of antidiuretic material will not respond to hypertonic saline by a reduction in water diuresis, as in the Hickey-Hare test (5e). In those few who fail to respond to replacement pitressin therapy a renal tubular defect can be postulated. This may be congenital and familial or may be a manifestation of renal disease (5f-i).

#### *B. Nature of Renal Dysfunction in Diabetes Insipidus*

The clinical syndrome of diabetes insipidus, irrespective of its origin, results in the output of urine of low specific gravity, i.e., 1.001 to 1.003 or 1.004, in daily volumes as high as eight or ten liters. In traditional terms this has been taken to indicate that filtration at the glomerulus and proximal tubular function are normal whereas the reabsorption of filtrate water in the distal tubules is diminished. If this be the actual fact, then these large urine volumes represent the loss of about one-half of the filtrate which has not been reabsorbed in the proximal portion of the nephron. Actually, the traditional partitioning of reabsorption between the two tubular segments has been questioned by some workers (6) and evidence has been advanced indicating that tubular secretion of water can also occur (7a, b). Hence, it is probably wiser to look upon diabetes insipidus as representing increased renal water output as a consequence of a diminished reabsorption, and possibly even a secretion of water, involving one or both segments of the tubules.

#### *C. Status of Electrolyte Metabolism in Diabetes Insipidus*

The low solute content of the urine and the virtually normal levels of electrolytes in uncomplicated diabetes insipidus when free access to water has been permitted (8) suggest that the control of solute output is unimpaired in this entity. Yet a number of workers have noted that the administration of pitressin to normal subjects and to patients with diabetes insipidus can result in an increased output of sodium and of chloride (9a, b). It has been suggested that this indicated contamination of the pitressin with anterior pituitary hormones. More recent studies, however, have iden-



tified this as an indirect response to this particular antidiuretic substance. Thus, the administration of pitressin and of water without electrolytes in sufficient amounts expands body fluids and lowers concentrations. This in turn produces a diuresis of sodium, chloride, and water and may therefore be looked upon as a mechanism which attempts to restore the volume of body fluids, even though concentrations may be lowered in the process. In the post-treatment phase excess water is eliminated and sodium and chloride are conserved (9c-e). Hence the so-called natriuretic and chloruretic response to pitressin appears to be an indirect mechanism activated by changes in body fluids induced by this hormone. This interpretation is supported by the finding that pitressin administered without water retention does not induce this response.

#### *D. Amelioration of Nonpsychogenic Diabetes Insipidus without Recourse to Pitressin*

It has been noted in animal experiments that total hypophysectomy does not produce the degree of diabetes insipidus which develops after injury to the posterior hypophyseal-hypothalamic apparatus. As a matter of fact only a transient polyuria of about one week's duration ensues. It has also been found that well-established diabetes insipidus diminishes in intensity following removal of the anterior hypophysis or thyroid (10a-c). Clinically, a number of reports describe decreases in the urine volume of diabetes insipidus patients not given specific replacement therapy (11a, b). The studies of Leaf and his collaborators indicate that in their patient the amelioration in symptomatology was mediated through a decreased intake of food and electrolytes secondary to anterior pituitary insufficiency. This diminished the urinary solute load and decreased the water exchanges without any change in the fundamental defect, i.e., in the inability of the patient to elaborate a concentrated urine. The absence of beneficial effects of growth hormone, thyroxine, or cortisone excluded the possibility that correction of endocrine deficiencies of this type was responsible for the clinical improvement. Raising the urinary solute load resulted in an exacerbation of the symptoms of the disease. These findings identify therefore one mechanism which influences the intensity of the clinical manifestations of this syndrome.

## **II. Antidiuretic Substances and Edema**

It has been suggested on the basis of bio-assay of urine or of blood that levels of antidiuretic material are increased in congestive heart failure, in cirrhosis with ascites, in nephrosis, and in pregnancy (12a-d). In general these findings have been taken to indicate that the retention of water and of salt which occurs in these patients is caused or aggravated by these sub-

stances. More precise assay technics however have revealed that insofar as blood is concerned there is no necessary correlation between levels of these materials and the presence or absence of edema (12e-g).

At present it appears justifiable to look upon the above findings as indicative of a disorder of mechanisms which regulate body fluid volume and composition. This view is obviously more inclusive than the original attempts to correlate levels and clinical manifestations but it still does not provide the reasons why in certain disease entities disorders of the tonicity and volume of body fluids are perpetuated.

### III. Body Fluid Derangements with Cerebral Injury

#### A. *Hypernatremia as a Consequence of Disordered Thirsting Mechanisms*

Experimentally produced hypothalamic injuries in rats result in obesity by virtue of increased appetite and chronically decrease the intake of water, i.e., "hypothalamic hypodipsia" develops (13). This results in higher sodium levels as a manifestation of chronic dehydration. Possible clinical counterparts of those experimental studies have also been reported with chronic hypernatremia present in patients with cerebral disease (14a-f). In both the animal and the human subjects the elevated levels of sodium persisted, despite free access to water, without any complaint of thirst. This finding suggests that the cerebral lesion deranged or injured the thirsting mechanism which regulates fluid intake (15a-f). These patients are not to be confused, of course, with those who have been deprived of water by virtue of neglect, loss of consciousness, etc. following a cerebral vascular accident, even though hypernatremia does develop. In this latter group one is dealing with simple dehydration with no evidence that the patient has any abnormality of the thirsting response *per se* (16a-c).

#### B. *Sodium Wastage*

In a small group of patients with encephalitis, bulbar poliomyelitis, or cerebral vascular accidents, sodium wastage not responsive to adrenocortical type steroids was encountered in the absence of renal disease (17, 14f). In some of the patients this appeared to be a temporary derangement during the acute phase of the disease. The actual mechanisms involved have not been identified. It is clear that injuries in the higher centers can modify renal function in animals and that denervation of a kidney alters blood flow, filtration rate, and tubular function (18a-c). These studies do not establish nor do they exclude the possibility that a direct neural connection exists between the brain and the kidneys which could mediate this or other abnormalities of sodium excretion. It has been suggested therefore that this syndrome might be attributable to dysfunction of such a tract (19a, b). This type of disorder is not to be confused with the chronic hyponatremia

which develops in the course of meningeal tuberculosis and represents generalized hypotonicity probably secondary to chronic decrease in the osmotically active constituents within cells (19b).

SUMMARY: Injury to the hypophyseal-hypothalamic mechanisms which decreases the supplies of antidiuretic substances produces diabetes insipidus. A similar syndrome may develop by virtue of disordered thirst mechanisms, as in emotionally disturbed individuals or as a consequence of congenital or acquired renal tubular unresponsiveness to the antidiuretic agent or agents. The fundamental defect in the nonpsychogenic forms consists of an inability to elaborate a concentrated urine. This is emphasized by the fact that a seeming amelioration of the syndrome occurs as a consequence of decrease in the load of solute presented to the kidneys for excretion. The natriuretic and chloruretic effects of posterior pituitary preparations appear to be secondary manifestations, and can be taken to represent an attempt to restore volume to normal following an initial undue expansion. At times brain disease or injury in areas other than the hypophyseal-hypothalamic axis is associated with undue retention or losses of sodium.

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## *Chapter 20*

### **PEDIATRIC FLUID DISORDERS AND THEIR THERAPY**

In the material which makes up the preceding chapters general and specific information concerning body water and electrolyte metabolism has been reviewed with reference to pertinent experimental data and to clinical problems in general. In this chapter some of the particular problems which confront the pediatrician will be discussed.

#### **1. The Development of a Rational Philosophy of Fluid Therapy in Infants**

For a number of years now workers in this country and abroad have directed their attention to the metabolism of water and electrolytes in infants and young children. The studies of Camerer and Söldner, Widdowson and McCance, and others indicate that in the early months of life the total body water and the body chloride are present in amounts which are relatively greater than those found in older children and adults (1a-k). The investigation of renal function by workers such as Barnett, Rubin, McCance and their contemporaries have revealed a variable maturation of renal function as reflected in indices of glomerular and tubular activity (2a-s). Thus the glomerular filtrate rates relative to body surface area are low, and an even greater reduction is present in some, but not all, of the secretory and reabsorptive functions of the tubules. External and internal transfers of the chief electrolytes in particular disease entities have occupied the attention of Gamble, Darrow, Butler, and Talbot as well as a host of colleagues in pediatric and nonpediatric fields (3a-j). All of these workers have contributed directly or indirectly to the formulation of a practical approach to fluid therapy which would meet the needs of the general practitioner and pediatrician. This will now be described in some detail with particular emphasis on the views of Butler, Talbot, and Darrow.

## II. Predominant Types of Fluid Disorders in Pediatric Practice

The most common fluid problem encountered by a pediatrician is acute dehydration and acute electrolyte depletion; excesses of water or electrolytes occur far less frequently. Two important differences distinguish these developments from similar disorders in adults: deficits and excesses are incurred more rapidly in children and such deficits or excesses are usually not complicated by a background of arteriosclerosis, congestive failure, or intrinsic renal disease.

Acute dehydration occurs in its least complicated form in the infant who has been deprived of water and other fluids by neglect but who is otherwise well (fig. 20-1) (4a, b). On the other hand the combination of dehydration and electrolyte depletion is much more apt to develop in the vomiting, diarrheal, or sweating infant (fig. 20-2 and 20-3) (5a-m) or in the infant or older child with intrinsic disease of the kidney, diabetic acidosis and coma, or adrenal cortical insufficiency with or without adrenogenital syndrome as discussed in chapter 18 (6a-j). Finally, excesses of water and electrolytes such as sodium, chloride, and potassium develop either with the administration of these substances in excess of the limits of the excretory or other regulatory mechanisms which are operating normally, or as a consequence of a disorder of these homeostatic adjustments which can then lead to undue retention of constituents taken in usual amounts (3c-e). The first of these is usually physician-induced whereas the latter group tends to develop spontaneously in patients with renal, cardiac, hepatic, or endocrine disorders.

## III. The Practicalities of Fluid Therapy in Infants and Young Children

The pediatrician should have clearly in mind the principles underlying resolution of the following questions: when should parenteral fluids be used? which fluids? how rapidly, via what routes, and for how long? General answers which should in the long run prove far more valuable than specific prescriptions are advanced in the paragraphs which follow.

### A. *Indications for Parenteral Fluids*

Parenteral fluid therapy is indicated whenever infants or young children are incapable of taking and retaining an adequate intake via the gastrointestinal tract as a result of anorexia, loss of consciousness, vomiting, diarrhea, surgical procedures, et cetera. As currently contrived, parenteral therapy is at best a temporary and inadequate makeshift for a complete diet. It should be used therefore only to prevent or to cancel deficits when an oral intake is not feasible.

Patient J.F. Diarrhea, fever, and dehydration  
Therapy

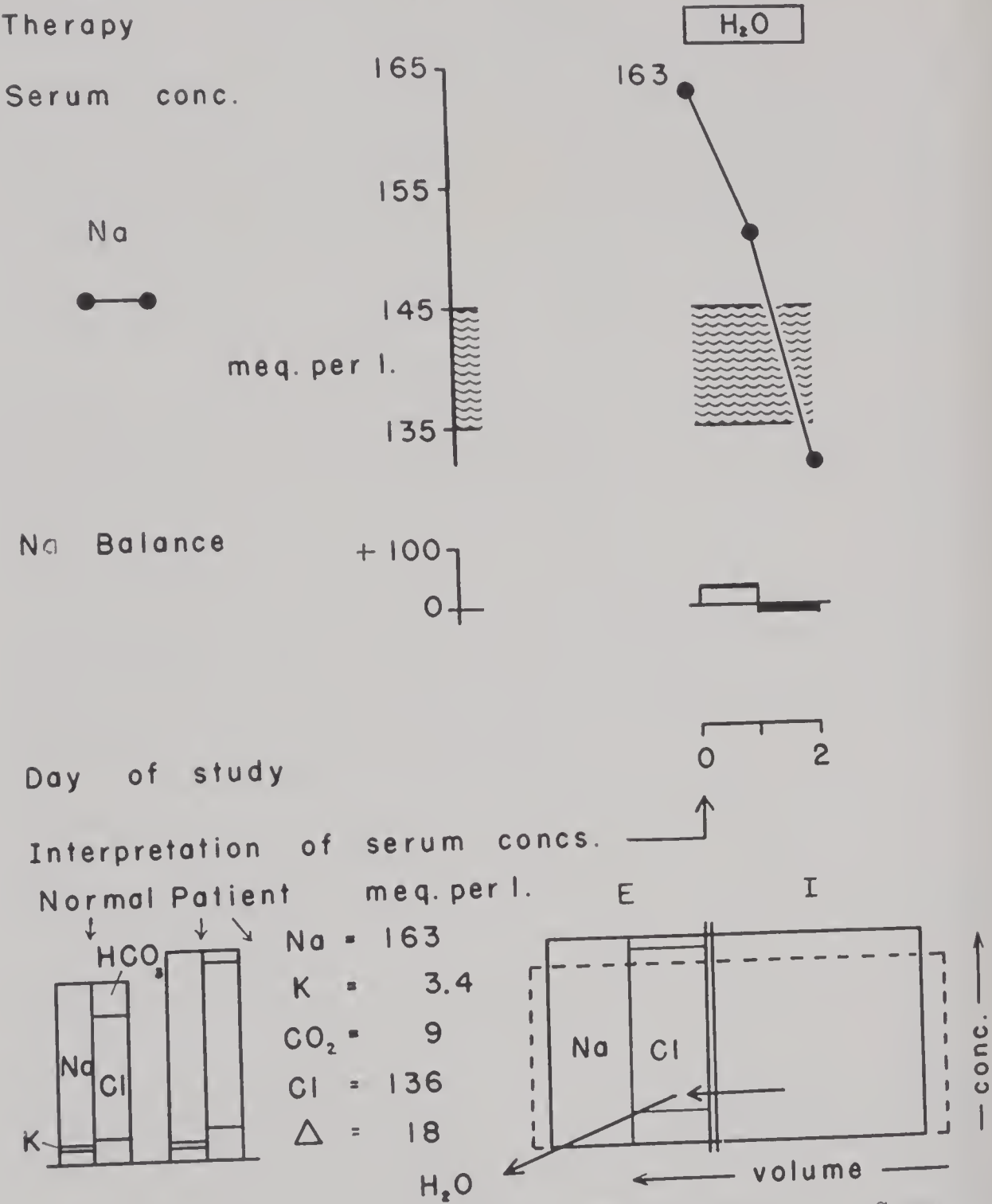


FIG. 20-1. BODY FLUID DEFICITS IN DIARRHEA AND DEHYDRATION. SERUM CONCENTRATION: HIGH SODIUM, HIGH CHLORIDE, LOW CARBON DIOXIDE

Clinical data and diagnosis. J. F., a 6-weeks-old male infant with diarrhea, fever and low fluid intake, responded well to administration of large amounts of water (as five per cent glucose) intravenously without a negative sodium balance.

Interpretation of serum concentration at start of day one: *Body fluid pattern:* Deficit of water in relation to salt: contraction of volume of both extracellular and intracellular phases with elevation of total electrolyte concentration (hypertonicity). Metabolic acidosis (low carbon dioxide and bicarbonate).

*Physiologic mechanisms:* During relative water deprivation, obligatory loss of hypotonic body fluid as insensible water and sweat through lungs and skin. Bicarbonate displaced by chloride and undetermined anions, owing to renal insufficiency and possibly ketosis of starvation. (From Squires and Elkinton (4b).)



B. The "Ideal" Type of Parenteral Fluid and its Dosage

The composition of the parenteral fluid depends upon whether the normal regulatory or homeostatic mechanisms are or are not functioning properly. If they are essentially intact, the current trend is toward the prescription of a dilute fluid which contains glucose, together with sodium, potassium, and chloride in amounts which are adequate for significant replacement if such is needed and which, if not needed, can be readily and safely excreted. Phosphate and metabolizable anions such as lactate are usually also included. The glucose provides calories, and thereby prevents ketosis as a consequence of overmobilization of body fat, and minimizes the breakdown of protein. The electrolytes in such a dilute solution make up for whatever moderate though limited losses may be occurring in sweat, urine, stool, et cetera. The dilute forms in which such solutions are used still provide adequate amounts of water for replacement of insensible losses through the

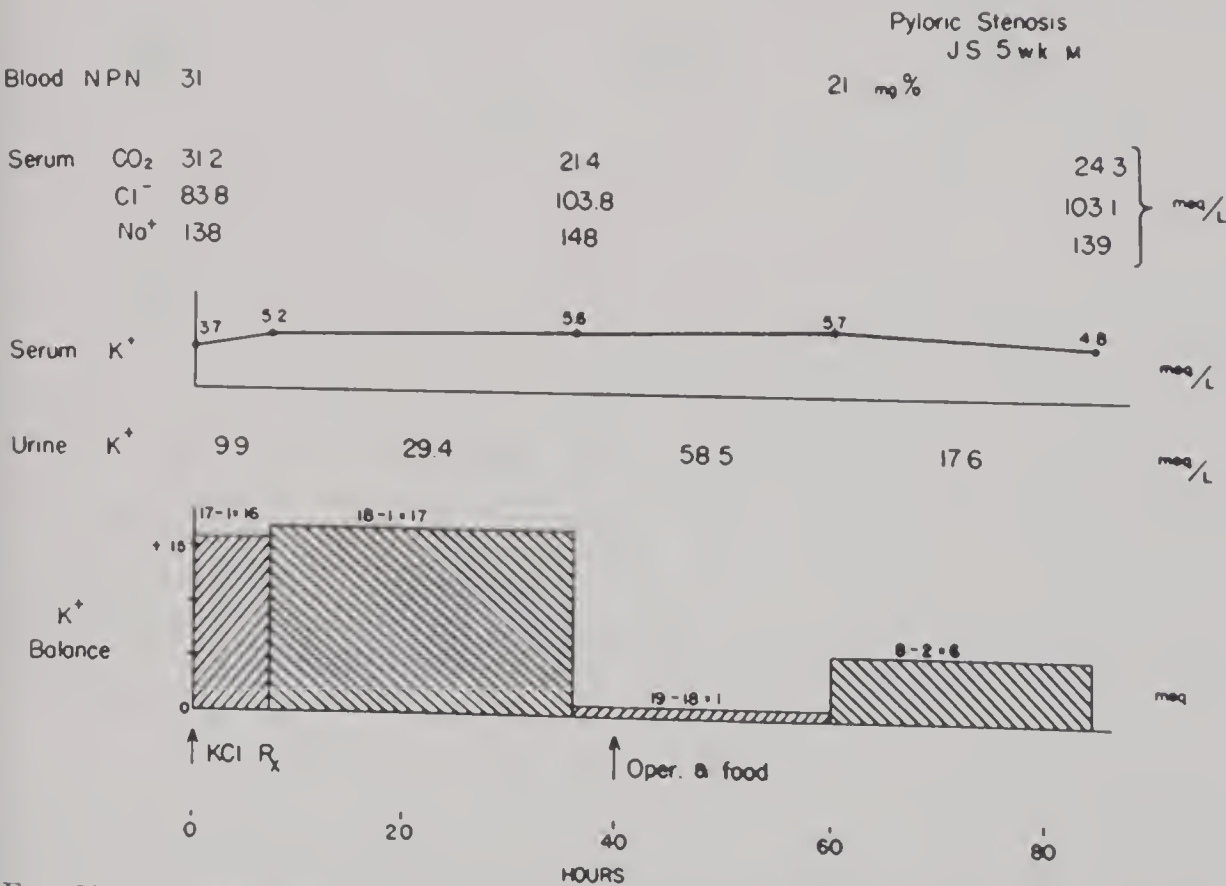


FIG. 20-2. SERUM ELECTROLYTES, URINARY POTASSIUM EXCRETION AND POTASSIUM BALANCE IN PYLORIC STENOSIS

This infant was admitted with hyponatremia and metabolic alkalosis secondary to losses of chloride and of potassium. Sodium level was not outside the range of normal. With therapy significant amounts of potassium were retained even though the urinary output of this ion rose. Serum potassium levels increased, while the serum level CO<sub>2</sub> content, chloride and sodium returned to normal. Urinary potassium rose and retention decreased sharply in response to operation in accordance with the changes discussed in chapter 21. From Danowski *et al* (6b).

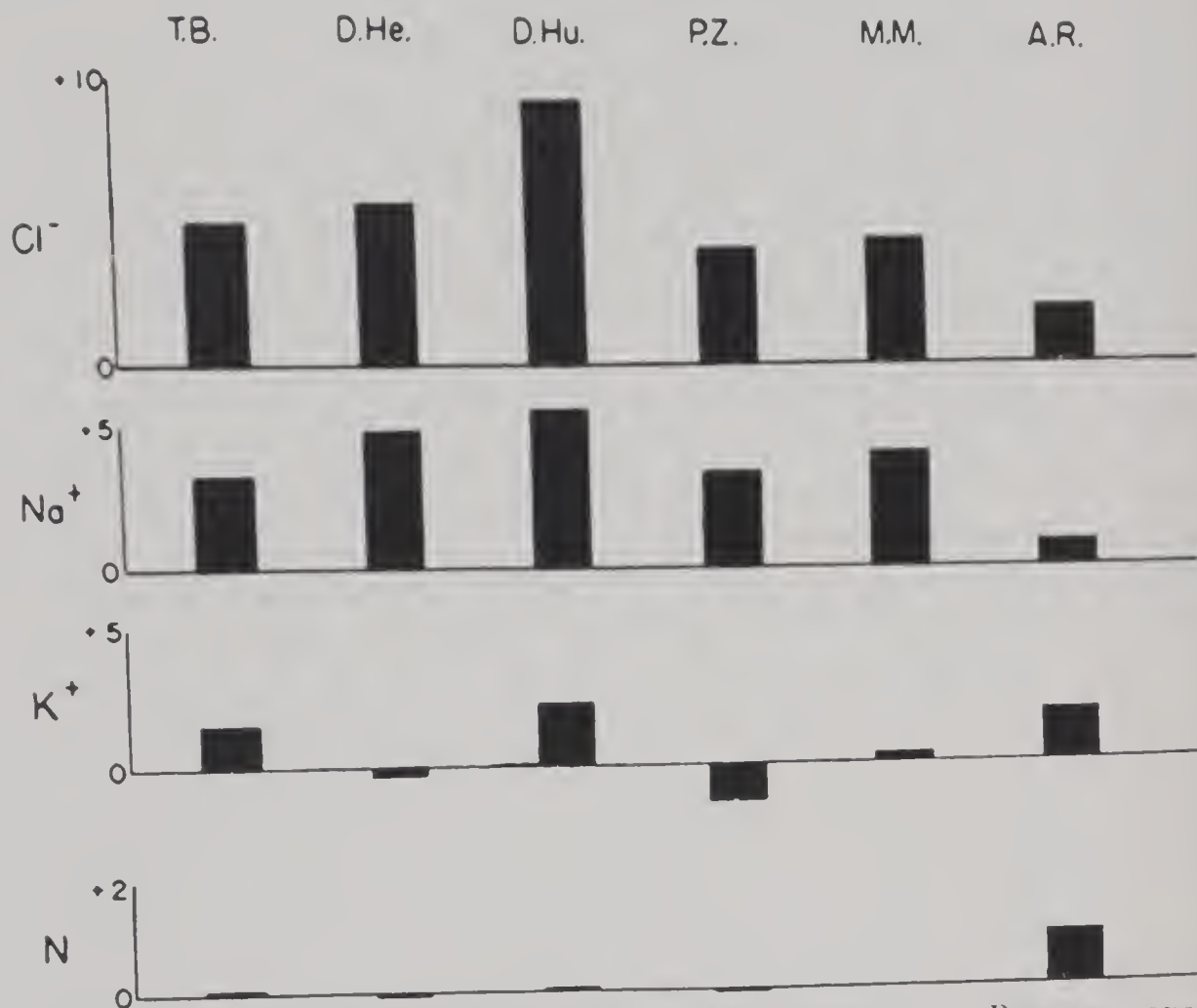


FIG. 20-3. RETENTION OF ELECTROLYTES AND NITROGEN DURING RECOVERY FROM PYLORIC STENOSIS OR INFANTILE DIARRHEA

Balance data are expressed in terms of mEq. per kg. of body weight per 24 hours in the case of the electrolytes and in grams in the case of nitrogen.

Infant A. R., age 14 months, retained significant amounts of nitrogen during recovery from protracted diarrhea together with positive balances of Cl, Na and K. In the other 5 infants recovering from pyloric stenosis the largest positive balances were usually seen in the case of chloride; the retention of Na was less. K balances were positive in only 3 of the infants while nitrogen retention was minimal. (From Danowski *et al* (5a).

skin and lungs, as well as for the excretion of unnecessary electrolytes via the kidney. In other words therapy with dilute fluids of the various types which have been suggested and used has been based upon the reasonable belief that if the regulatory or homeostatic mechanism of the body is not exceeded, the body will make all of the necessary adjustment, provided it is given suitable raw materials. The two extremes of too little or too much of any particular constituent can be avoided by adherence to the "Floor" and "Ceiling" values suggested by Talbot, Crawford and Butler (3e). These are presented in table 20-I and figure 23-1.

The solutions shown in table 20-II suggested by these same authors,

given at a rate of approximately 900 to 2700 cc. per 24-hour period per square meter of surface area, will encompass the floor and ceiling values cited earlier. Solutions of the same general type suggested by Butler, by Darrow, and others are listed in table 24-III (3c-i). It is obvious however that with a more rapid rate of administration the ceiling can be quickly surpassed even with these dilute solutions.

C. Route and Duration of Parenteral Therapy

Such dilute solutions should be given by vein. They should not be given subcutaneously since they are hypotonic to body fluids and will abstract extracellular electrolytes from the patient and produce circulatory collapse, as illustrated in fig. 7-4 (7a). This is akin to the removal of electrolytes which occurs when the gastrointestinal tract is lavaged with non-electrolytic solutions. Hyaluronidase will not prevent such sequestration of electrolyte (7b), though it will of course hasten absorption of the fluid. It is

TABLE 20-I.

HOMEOSTATIC LIMITS IN PARENTERAL FLUID THERAPY*		
	'Floor'	'Ceiling'
Glucose	75 grams/sq.m./24 hrs.	350 grams/sq.m./24 hrs.
Sodium	10 mEq. /sq.m./24 hrs.	225 mEq. /sq.m./24 hrs.
Potassium	10 mEq. /sq.m./24 hrs.	225 mEq. /sq.m./24 hrs.
Phosphorus	0.3 grams/sq.m./24 hrs.	2.0 grams/sq.m./24 hrs.
Water	0.7 cc/m.osm. solute	10.0 cc/m.osm. solute

\* From Talbot et al (3e,8)

TABLE 20-II.

SAMPLE MULTIPLE ELECTROLYTE SOLUTION (after Talbot, Crawford and Butler (3e))				
Na <sup>+</sup>	40	mEq/l	of 5% glucose	
K <sup>+</sup>	35.5	"	"	"
Cl <sup>-</sup>	40	"	"	"
Lactate	20	"	"	"
Phosphate	15.5	"	"	"



TABLE 20-III.

APPROXIMATE RELATIONSHIPS OF BODY WEIGHT		
BODY WEIGHT		SURFACE AREA
(Kilograms)	(Pounds)	(Square Meter)
2	4.4	.15
5	11.0	.25
10	22.0	.45
15	33.0	.6
20	44.0	.8
30	66.0	1.05
40	88.0	1.3

imperative therefore to avoid the subcutaneous route when hypotonic solutions are used.

Insofar as duration of parenteral fluid therapy is concerned it is universally agreed that it should be interrupted as soon as an adequate oral intake is achieved.

*D. Use of the Surface Area in Calculating Dosage of Parenteral Fluids*

Any program of fluid therapy must take into account the fact that infants and children vary in body size and weight. As indicated above, the current trend is to express needs and replacements in terms of the body surface area. Most textbooks of pediatrics have conversion tables based on height and weight, but for practical purposes a table based on weight alone suffices. Thus at the Massachusetts General Hospital (8) the conversion factors shown in table 20-III are used.

**IV. Limitations of Dilute Fluids in Parenteral Therapy**

The types of fluid described in the preceding section have two limitations: they are inadequate for the rapid replacement of large deficits of body electrolytes and they cannot be used in patients with disordered regulatory mechanisms, such as those undergoing surgery or anaesthesia or ill with far-advanced renal failure, congestive failure, cirrhosis, adrenocortical insufficiency, diabetes insipidus, et cetera.

Rapid replenishment of greatly depleted body stores will require more concentrated solutions. Thus in salt depletion 0.9 per cent or even higher concentrations of sodium chloride in glucose or in water can be used, though care must be taken not to exceed the renal excretory limits for sodium as described earlier. Similarly with extreme potassium deficiencies such as

those which develop in diarrheal infants (5d-g), in diabetic coma (6c-g), in pyloric stenosis (5a, b), more concentrated solutions of potassium, up to 70 or 80 milliequivalents per liter, can be used (5a-g). The precautions to be taken against potassium intoxication described in chapter 7 should be put into routine practice, i.e., controlled rates of administration in all patients to avoid hyperkalemia and withholding of potassium until the renal excretory status and the serum levels of the ion have been evaluated. In the latter regard the direct writing electrocardiograph can be particularly helpful since peaking of the T wave points to rising concentrations of potassium (chapter 8).

Limitations of homeostatic regulation develop transiently as a result of anaesthesia and medication (such as morphine or demerol) and are present in more or less permanent form in the disease entities cited earlier, i.e., in those in which the renal, hepatic, cardiovascular or hormonal systems are involved by disease. In the case of anaesthesia and surgery the input of the dilute solutions should be limited to some 1500 ml./sq. meter/24 hours in contrast to the usual ceiling of 2700 ml. (3c, 8). In the special situation therapy has to be tailored to fit the particular patient. All of these disease entities have been discussed in detail in the preceding chapters.

**SUMMARY:** The current emphasis upon pediatric fluid therapy is upon the provision of water and solutes in amounts sufficient to permit replacement of deficits without overburdening excretory and regulatory mechanisms. It is recognized that major disease involving the kidney, heart, adrenal cortices or certain preoperative or operative procedures compromise the ability of the body to make necessary adjustments in body fluid composition and to dispose of water and solute loads. In most instances of simple dehydration or depletion the provision of an intake of hypotonic fluid in accordance with the size of the infant, as reflected in the body surface area, will permit adequate and safe replenishment.

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## *Chapter 21*

### **BODY FLUID PROBLEMS IN SURGICAL PATIENTS**

Many of the problems encountered by the internist and pediatrician are also present in surgical patients. Thus starvation, dehydration, sweating, renal insufficiency and congestive failure are all potential concomitants of surgical disease entities. The surgeon is in addition faced at times with hazards related to the particular surgical problem or to its therapy. These special problems include the uncomplicated pre- and postoperative fluid prescription, the relief of gastrointestinal obstruction by suction, the replacement of deficits incurred through trauma, burns, vomiting, ileal or other gastrointestinal drainage, the therapy of shock, the control of adrenocortical manifestations, the care of patients subjected to adrenalectomy or hypophysectomy, and finally the preparation of patients for major cardiovascular surgery.

#### **I. The Metabolic Responses to Surgery**

It is obvious from the detailed studies of Moore, of Hardy and of others, that surgical procedures with the concomitant anaesthesia produce a train of metabolic changes (1a-f). These are set in motion by the events attendant upon surgery, i.e., by the trauma of section and dissection, and by the starvation and immobilization which are present in greater or lesser degree. It is likely that there are in addition other as yet unidentified factors, psychogenic and physiologic, which also serve as stimuli. This mass of known and unknown stimuli in turn sets off responses in which the role of at least the adrenal cortex has been identified. Again, it is highly probable that other endocrines, other tissues, and other mechanisms also participate in the production of the final net effect. The end result of the interaction of this mass of stimuli and the group of responses includes the

following series of changes:

- a) elevation of the body temperature
- b) rise in the pulse rate
- c) diminution in urine volume
- d) increased urinary output of nitrogen
- e) increased urinary output of potassium
- f) decreased urinary excretion of sodium
- g) loss of weight suggestive of a decrease on body fat

The finding of an increased urinary output of steroids together with the demonstration of a variable decrease in circulating eosinophils points to increased adrenocortical activity. In accordance with the known effects of adrenocortical steroids as described in chapter 18 this could by itself explain the sodium retention, and the nitrogen and potassium losses in the above catalogue of events. It could also be responsible for part if not all of the decrease in urine volume and increase in fat utilization. These changes are evident for three to five days in uncomplicated surgical cases and are followed by reconstitution of body components. Thus, nitrogen and potassium are retained while a diuresis of sodium and water occurs; body weight rises (see fig. 3-11). The immediate postoperative retentions of water and sodium, as well as the later retention of sodium, are illustrated in fig. 21-1.

It is particularly important that this *normal* response to surgery be recognized and that unnecessary attempts to overcompensate for its effects be avoided (lg). Actually it is self-limited and presents a problem only when it is superimposed on pre-existing derangements or when it is prolonged by complications of the surgical procedure or in the underlying disease.

In patients with pre-existing deficits these effects of surgery may be less pronounced, possibly because the patient has already responded to the stimuli which resulted in the deficits or because the response mechanisms are fatigued. This does not mean however that in these patients surgical procedures are less traumatic but rather that the normal responsiveness to such stimuli is lacking. An excellent argument can therefore be advanced for replenishment of body constituents prior to surgical intervention. If this is not feasible, supplementation of endogenous adrenocortical steroids with cortisone or hydrocortisone is indicated.

The deferral of recovery by virtue of surgical or disease complications will also alter the pattern of metabolic response. New stimuli are introduced, the recovery phase is deferred, and starvation and immobilization are prolonged. The resultant derangements of body homeostasis are then aggravated by renal or circulatory failure and by losses of body fluids through drainage or exudation, or via injudicious prescription. The prevention and avoidance of these sequelae are discussed in further detail in the sections which follow.

## II. Fluid Therapy in Relation to Operative Procedures

In elective operations in patients previously well, fluid is prescribed only for the replacement of concurrent losses. In uncomplicated situations these consist of the insensible loss of water via the skin and lungs and the urinary output. This is graphically presented in figure 21-2 taken from Abbott. As pointed out in Part II of this book, about 1500 cc. of 10 per cent glucose in water will meet these needs since we can count on renal conservation to prevent undue sodium losses. If convalescence is protracted or complicated and urinary function is intact, potassium salts should be added in amounts sufficient to provide a daily intake of 80 to 160 milliequivalents of the ion. This will replace the urinary losses of this ion which continue unabated in ill patients despite a lack of an adequate intake. One of the solutions described in chapter 24 will provide these amounts in a reasonable volume.

Obviously in patients in whom preoperative deficits of water or of the chief electrolytes, i.e., sodium, chloride, or potassium, have developed, replacement should precede surgery. There is unfortunately no simple rule of thumb which will accurately predict the patient's replacement needs (1h). Certain helpful experiences in deciding upon orders of magnitude are discussed in detail in chapter 23.

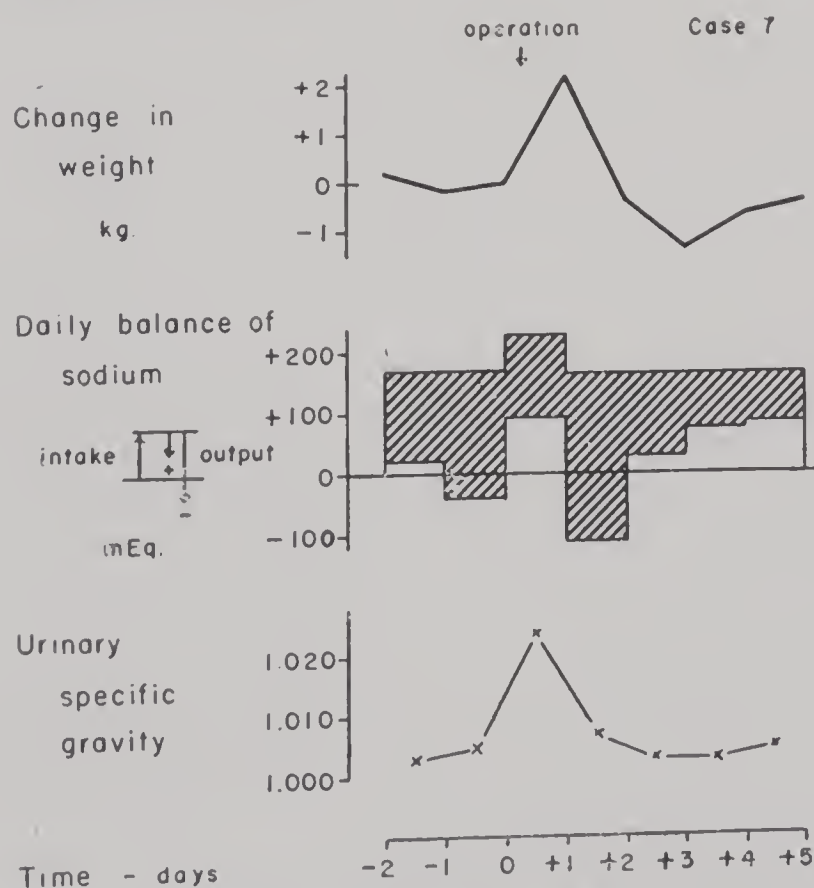


FIG. 21-1. POSTOPERATIVE RETENTION OF WATER AND SODIUM

The primary retention of water (antidiuresis) and of sodium on the day of operation is followed by a separate and later phase of sodium retention during the 2nd to 4th postoperative day. (Data from LeQuesne and Lewis (12c).)



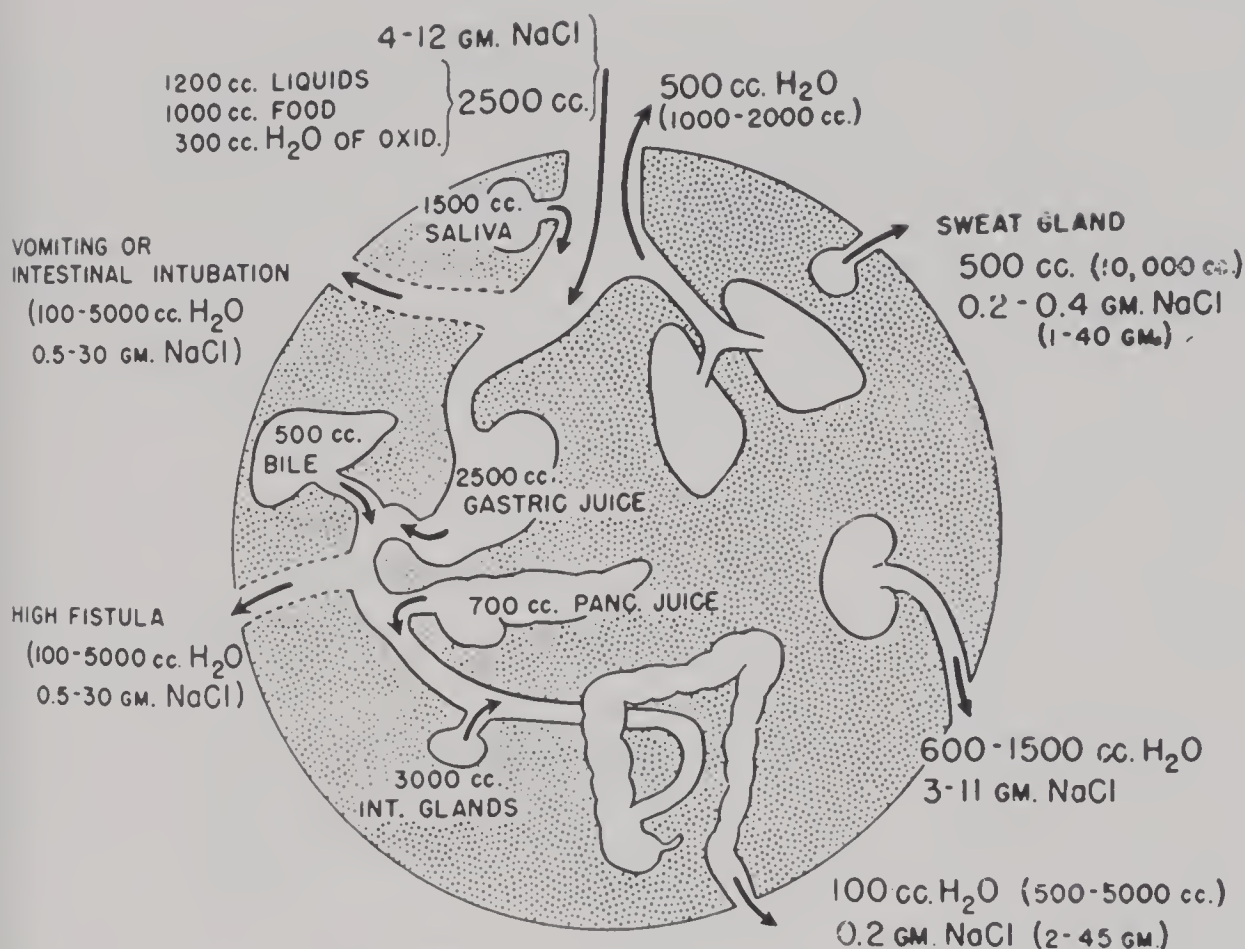


FIG. 21-2. ORDERS OF MAGNITUDE OF POSSIBLE FLUID LOSSES VIA THE GASTROINTESTINAL TRACT AND RELATED ROUTES  
From Abbott (1i)

In terms of general principles it is well to keep in mind, a) that the daily input must exceed the concurrent losses if deficits are to be replaced, b) that in terms of volume the ordinary intravenous input should be confined to three liters per day in adults but that with drainage, vomiting or sweating five or six liters can and must be given, c) that in an adult deficits may reach as high as 114 ml. per kg. of body weight in the case of water, and 32.5 and 21.7 milliequivalents per kilogram of body weight, respectively, in the case of sodium and potassium (see chapter 23), d) that in replacing water deficits solutions which contain sodium will only aggravate the hypertonicity and preempt water for urinary excretion, e) that in sodium replacement physiologic or 0.9 per cent sodium chloride usually provides too great an excess of chloride and hence  $\frac{1}{6}$  molar lactate or Ringer's lactate are often preferable, f) that the administration of potassium is safe only when renal function is adequate, i.e., BUN or NPN is not elevated, urine is being elaborated, and the rate of inflow is restricted to approximately 35 milliequivalents per hour, g) that the kidney will adjust within limits, but only within limits, for errors of judgment in the administration of the chief body fluid constituents; conversely, inadequate renal function

Patient: T.B., 63 $\sigma$ w, Pyloric obstruction: electrolyte depletion, metabolic alkalosis

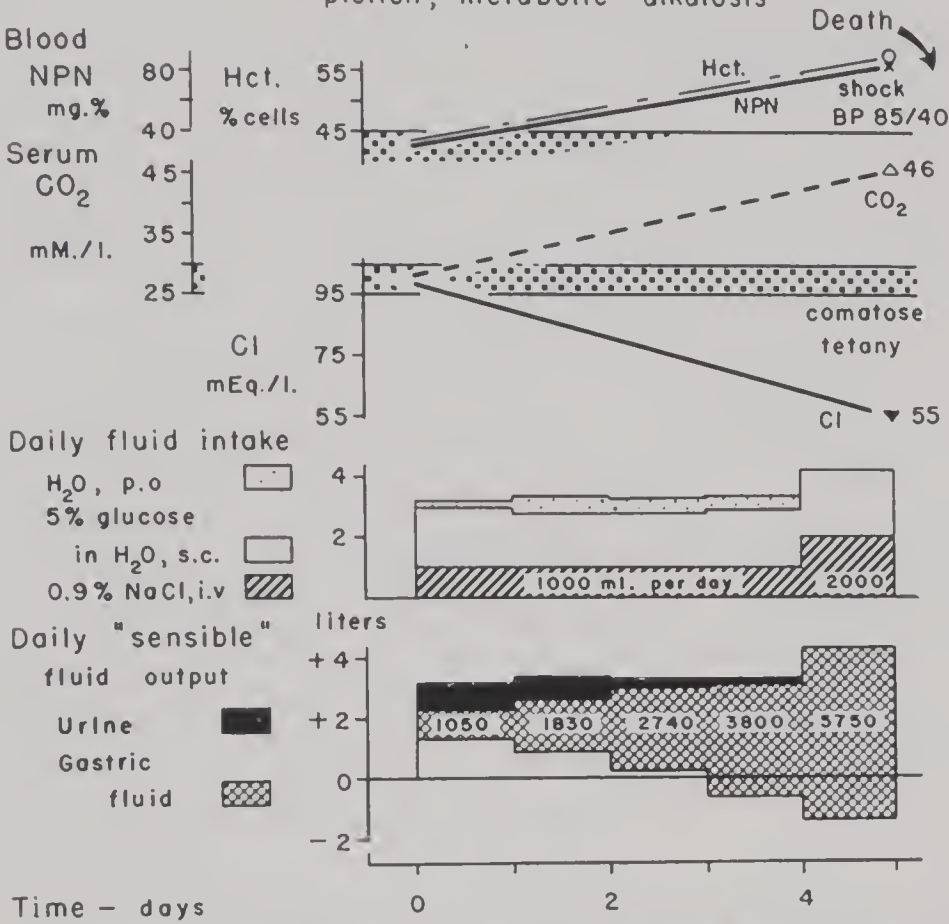


FIG. 21-3. POSTOPERATIVE GASTRIC FLUID LOSS WITH ELECTROLYTE DEPLETION AND DEATH

The routine parenteral fluid therapy failed to replace adequately the water and electrolytes contained in the increasingly greater amounts of gastric fluid removed by suction from a non-functioning gastrojejunostomy. The preventable result was dehydration, extracellular electrolyte depletion, metabolic alkalosis and tetany, irreversible shock, and death. (Elkinton *et al.*, unpublished case study in another hospital.)

greatly increases the need for precise fluid prescriptions since these compensating adjustments are limited or lost, h) that the route of administration is especially important since salt-free hypodermoclyses produce temporary salt depletion (see fig. 7-4) and since the rates of absorption from subcutaneous tissues are unpredictable, even though hyaluronidase does accelerate the process, and finally i) that the status of the circulation and of the kidney, i.e., shock, congestive failure, lower nephron nephrosis, et cetera, can be an extremely important factor limiting the efficacy of replacement fluids.

### III. The Problem of Gastrointestinal Fluid Losses in Surgical Patients

The prevention or replacement of deficits occasioned by losses of gastrointestinal secretions is one of the most frequent problems faced by the

surgeon (1i). With regard to the former it is usually recognized that continuation of an oral intake in a vomiting patient, even when limited to ice chips, only aggravates the vomiting and the electrolyte losses (2a). Total withdrawal of all oral intake and maintenance on parenteral fluids will stop vomiting in many patients. However, those with marked upper gastrointestinal tract obstruction will continue to pour out large amounts of fluid even though oral intake is cut off (2b). It is customary to intubate these and drain off the secretions with or without concomitant lavage. Recourse to the latter may give rise to major problems.

First, if lavage is employed, distilled water or aqueous electrolyte-free solutions must be assiduously avoided, since they inevitably produce electrolyte depletion due to diffusion of ions into the salt-free fluid. Such solutions have the same effect as water by mouth, i.e., electrolytes pour into the fluid which reaches the stomach and are lost in subsequent drainage or vomitus. The net effect is sodium depletion, circulatory collapse, and renal failure as detailed in chapters 6 and 7 and illustrated in figures 6-5, 7-2, 7-4. Hence lavage solutions should approximate extracellular fluid in composition, or at least be limited to 0.9 per cent saline if electrolyte depletion is to be avoided.

Second, if lavage solutions are used, particular care must be taken to quantitate the intake and output since only in this way will the magnitude of the body fluid loss become known. Without such knowledge maintenance or replacement prescriptions of body fluids cannot be intelligently devised; with it replacement volumes can be readily estimated. The composition of such replacement fluids will depend in turn upon the particular gastrointestinal secretions which are lost and the concomitant exchanges via routes other than the gastrointestinal tract.

In table 21-I the electrolyte content of secretions obtained from various parts of the gastrointestinal tract is listed (2c-h). It is to be noted that sodium is about equally prevalent throughout, that chloride is highest in gastric juice and diminishes distal to the pylorus as bicarbonate content rises, and that the concentrations of potassium in the various secretions are several fold higher than those present in extracellular fluids. The range of volumes observed clinically is shown in figure 21-2. As discussed in chapter 7, however, it should be kept in mind that hypochloremic alkalosis points to the existence of either a predominant chloride deficit or to a cellular deficiency of potassium, alone or in combination. This distinction is generally made in the reports of potassium deficiency in surgical patients (3a-z) and the importance of potassium deficits in the genesis of experimental paralytic or adynamic ileus is often cited (4a-f). These findings together with those of Darrow and Susan Gower Smith indicating muscular necrosis (5a, b) and of Cannon showing the limitations in protein repletion which appear with potassium deficits (5c, d), amply justify the surgeon's



TABLE 21-I.

ELECTROLYTE CONTENT OF ORAL AND GASTROINTESTINAL SECRETIONS					Electrolyte Concentration in mEq./l.			
AUTHORS	SUBJECTS (#)	Secretion	No. analyses		Na <sup>+</sup>	K <sup>+</sup>	Ca <sup>++</sup>	Cl <sup>-</sup>
					(mEq./l.) Mean	(mEq./l.) Mean	(mEq./l.) Mean	(mEq./l.) Mean
					(max-min)	(max-min)	(max-min)	(max-min)
Dreizen	(2c) Arthritis	Resting saliva	24		20.6 ( 6-85 )	20.1 (14-32)		
		Stimulated saliva	24		38.0 ( 13-89 )	20.5 (15-30)		
Bernstein	(2d) Healthy young adults	Resting saliva			44 ( 16-78 )	20.4 ( 9-29 )	6.5 (4-8)	
		Overnight gastric	50		49 ( 19-70 )	11.6 ( 6-17 )	3.6 (2-5)	
		A.M. Gastric*	44-82		42 ( 16-59 )	9.7 ( 6-13 )	3.3 (2-5)	
		Gastric	9		66.5	13.7		100.6
Lesser & Pareira Lans et al.	(2e) Pre-op patients	Gastric			56 ( 21-82 )	12.6 ( 6-26 )		126 (76-157)
	(2f) Peptic ulcer (24)	Gastric	72		61 ( 24-91 )	10.2 ( 7-25 )		58 (39-110)
	Gastric Ca (13)	Gastric	48		72 ( 32-126 )	12.1 ( 5-25 )		56 (36-92 )
	p̄ Vagot. (4)	Gastric	13		136 ( 82-167 )	5.3 ( 2-9 )		98 (38-142)
	Resections (21)	Gastric	40		113 ( 46-117 )			104 (24-127)
	Nongastric pts. (41)	Gastric	64					

McGowan & Stanley	(2g)	Peptic ulcer	Gastric	12	( 20- 90)	( 5-19)	(0-2)	(80-152)
		Gastritis						
		Hypokalemia						
		Hypocalcemia						
		Met.alk; resp.acid						
Lockwood & Randall	(2h)	Surg. Patients	Gastric		60.4	9.2		84.0
					( 9-116)	( 0-32)		( 8-154)
			Small		111.3	4.6		104.2
			bowel		( 82-148)	( 2-8)		(43-137)
			Ileostomy		129.4	11.2		116.2
			(recent)		(105-144)	( 6-29)		(90-136)
			Ileostomy		46	3.0		21.4
			(adopted)					
			Caecostomy		52.5	7.9		42.5
			Bile		148.9	4.98		100.6
					(131-164)	( 3-12)		(89-18 )
			Pancreas		141.1	4.6		76.6
					(113-153)	( 3- 7)		(54- 95)

\* Obtained at intervals during 1 to 2 hours

attention to body potassium stores even though at present there is no experimental evidence that wound healing itself is compromised under such circumstances (6a, b). Postoperative gastrointestinal fluid loss with resultant electrolyte depletion and death, is illustrated in fig. 21-3.

The most precise type of replacement is based upon direct analyses of these fluids in the individual patients, supplemented by examinations of the urinary output and the blood and serum solute levels. In the absence of such balance data intelligent estimates can be made from a knowledge of the output volume, utilizing the average compositions as listed above. Serum levels are then particularly helpful in reflecting the adequacy of therapy.

#### **IV. The Recognition and Therapy of Shock in Surgical Patients**

It may not be amiss to point out that, as in medical patients, the simple presence of a normal blood pressure does not exclude cardiovascular collapse. In addition to the hypertensive patients who drop only to normotensive levels following dehydration, hemorrhage, trauma or burns, there are those who have marked impairment of circulatory efficiency without drop in blood pressure. In the latter group blood pressure readings remain normal by virtue of shunting or vasoconstriction which deprives tissues of their ordinary complement of blood flow and oxygen. Hence awareness of these adjustments must prevail if therapy is to be undertaken before the traditional signs of hypotension, weak and rapid pulse, mottled skin, et cetera, appear.

##### *A. Use of Crystalloids, Colloids, and Norepinephrine in the Therapy of Surgical Shock*

In shocked subjects the blood pressure can be restored by the intravenous infusion of saline or even of glucose, though glucose in water should not be used for this purpose, provided that these solutions are given in adequate volumes (7a). They are, however, not as efficient in this regard as are solutions which contain colloids, i.e., blood, plasma, human serum albumin, or plasma substitutes such as dextran, oxygelatin, and polyvinylpyrrolidone (see table 24-IV) (7b, c). The greater effectiveness of the latter group with regard to volumes needed and duration of response are in large measure ascribable of course to the fact that the macromolecules remain in the vascular system much longer than do crystalloids.

Experience is accumulating which indicates that norepinephrine can be used with benefit in those patients in whom even massive infusions of colloid fail to restore and maintain the pressure (8a). This agent constricts the vascular bed and thereby makes up for volume deficiencies. Studies in animals indicate that this does not compromise renal function, even though



dynamics are altered (8b); trials in humans suggest that it can be used for several days, 4 ml. of 1:1000 norepinephrine per 1000 cc. of saline or glucose given as necessary with ultimate uneventful recovery (8a).

*B. Lower Nephron Nephrosis, i.e., Acute Tubular Damage as a Complication of Surgical Shock*

It is generally recognized that anuria on the basis of acute tubular damage may supervene following a bout of hypotension. This subject is discussed in greater detail in chapter 12, but it should again be emphasized that excessive administration of glucose in water in an attempt to induce diuresis is a common and dangerous error. The surgeon must be equally alert, however, in identifying instances of less extensive injury of this type in which renal inefficiency rather than anuria appears. In such patients the NPN may rise in the face of a seemingly adequate or more than adequate urine flow, or evidences of electrolyte wastage may appear. All of these represent instances of tubular damage which is insufficient to block urine flow but which does disrupt renal function. Therapy of this disorder is also detailed in chapter 12.

## **V. Fluid Aspects of Adrenalectomy or of Hypophysectomy**

*A. Basis for Replacement Therapy Following Adrenalectomy*

Adrenalectomy as the sole or adjunct procedure for control of metastatic cancer or hypertensive vascular disease is now undergoing clinical trial (9a-c). The control of water and electrolyte metabolism following complete removal of the adrenals presents some problems even though certain fundamental principles are applied. Before discussion of these, however, it should be pointed out that in patients subjected to partial adrenalectomy, usually some functioning tissue is left.

In the chapter dealing with the adrenal cortex (chapter 18) it was pointed out that from the electrolyte-water point of view patients with classical Addison's disease show renal wastage of sodium, chloride and water. When the extracellular stores of these constituents become decreased, as a consequence of an intake inadequate to cover the urinary losses, the circulatory collapse of salt depletion appears. Prior to and concomitant with such circulatory collapse evidences of undue potassium retention, involving both the cellular and extracellular phases, are present. Usually the resultant hyperkalemia is not of sufficient magnitude to produce cardiac standstill.

These electrolyte changes are accompanied by disturbances in the intermediate metabolism of foodstuffs: the rates of absorption of sugars and other foodstuffs from the gastrointestinal tract are diminished, gluconeogenesis from amino acids and other precursors falls off, the block of peripheral utilization of glucose by adrenocortical steroids is removed, and glycogen

formation is decreased. The net effect of these changes is a pronounced tendency to hypoglycemia.

Most of the Addison's cases also show evidences of diminished androgenic secretion with loss of libido, decreased 17-ketosteroid excretion, and diminished muscle strength.

Hence from the medical viewpoint Addison's disease which develops spontaneously has always been regarded as an illness serious enough to jeopardize life, even during therapy. The addition of cortisone and hydrocortisone, Compounds E and F, to the usual program of desoxycorticosterone acetate therapy has improved the outlook. These patients now do quite well on an ordinary intake of sodium without potassium restriction, provided that extra amounts of cortisone are given during infections, surgery, etc. The totally adrenalectomized patients also do quite well on this type of regimen. Usually 2 to 5 mg. of DOCA and 25 to 50 mg. of cortisone are used each day. The former controls electrolyte and water metabolism while the latter corrects the abnormalities in the intermediate metabolism of foodstuffs (9a-c).

Our limited observations make us feel that the adrenalectomy cases do somewhat better than the spontaneous Addison's cases. This may be related to the fact that replacement therapy is instituted immediately following loss of the endogenous secretions, whereas in the spontaneous disease months and perhaps years may elapse with various degrees of untreated insufficiency.

### *B. Anterior Hypophysectomy and Its Effects*

The surgical removal of the anterior hypophysis is also being tested as a therapeutic procedure for metastatic or generalized cancer (10a-c). If this is successfully accomplished it removes the trophic or tropic hormones ordinarily elaborated by this endocrine, including the growth-diabetogenic factor, the hormones which stimulate the thyroid, adrenal cortex, the gonads, the mammary gland and possibly the melanophore factor. In patients with Sheehan's Syndrome or Simmonds' Disease in which destruction of the anterior pituitary has occurred the onset of symptoms relative to hypofunction of the target glands is insidious. The first signs, as pointed out in chapter 17, are apt to be those related to gonadal hypofunction, i.e., loss of libido, amenorrhea, etc.; hypothyroidism is next in order of frequency; adrenocortical insufficiency becomes manifest with stress situations and may not be evident under ordinary circumstances (10d). Hence, it is obvious that a lowered level of generalized endocrine activity supervenes without dramatic onset. This is compatible with a period of survival which is longer than the expectancy with most cases of metastatic neoplasm. If symptoms become troublesome, replacement therapy must be undertaken

with caution, since thyroid administration can provoke adrenocortical insufficiency.

## VI. Body Fluid Problems in Cardiac Surgery

It must be kept in mind that, even though the various surgical approaches to correction of congenital and other defects of the heart and great vessels are elective, the body fluids may or may not be normal prior to surgery. New steady states of distant or of recent origin are often present and the surgeon is faced with the problem of deciding whether an attempt should be made to correct these abnormalities prior to surgery. Experience is as yet limited in this field but what has been recorded together with certain general principles, permits intelligent treatment of this problem.

### *A. The State of the Plasma and Blood Volumes in Patients Undergoing Cardiac Surgery*

In anoxic cardiopulmonary disorders relative and absolute increases in red cell and in blood volume are usually present (11). In the congenital abnormalities of the heart the relative blood cell volume or hematocrit reaches up to 70 or 80 volumes per cent, values which are almost double those present in health. The withdrawal and processing of such blood, whether arterial or venous, amply illustrate that its viscosity is unduly high and suggests that the compensatory erythremia in response to anoxia has exceeded the optimal boundaries. Obviously the circulation of such a fluid represents an extra cardiac burden which may require relief. First, the possible benefits of lowering the relative hematocrit by withdrawal of whole blood and replacement of plasma should be considered. Second, maintenance of circulatory efficiency at maximal levels should be undertaken prior to, during, and after surgery by measures such as oxygen therapy, digitalization and judicious limitation of fluid therapy. Finally, the importance of avoiding prolonged surgery has been amply emphasized by the workers in this field.

### *B. The Possible Harmful Effects of Antecedent Regimens*

Many patients with cardiac lesions who develop symptoms or signs interpreted as indicative of decompensation are placed on sodium restricted regimens. These are at times supplemented by diuretics or by agents such as cation exchange resins. Hence the possibility is always present that such patients can develop sodium depletion. This is most apt to occur of course during intervals of extrarenal sodium loss as in sweat, vomitus or feces superimposed upon whatever urinary excretion of sodium may be present. Obviously such patients would enter upon surgery with the additional unnecessary burden of salt depletion with its attendant circulatory ineffi-



ciency. This possibility must therefore always be raised prior to actual surgery and the question resolved, insofar as it can be, by measurements of blood and serum solutes. In such patients the recent advent of an increased BUN or NPN together with hyponatremia virtually establishes the presence of sodium depletion and contraindicates surgery until such deficits are replaced. As has been pointed out in chapter 13, this form of hyponatremia is to be differentiated from the new steady state which develops in some instances of congestive failure and which is of extremely ominous portent. The identification of such individuals and the therapy indicated have been set forth in the chapter on Congestive Heart Failure. On the other hand a certain number of patients who have undergone cardiac surgery develop hyponatremia which appears to be transient and less grave. In such instances it seems probable that the altered levels of sodium are in great measure attributable to water retention, presumably secondary to limitations of the regulating mechanisms and perhaps aggravated by intake (12a-c). The possibility of an associated, though limited, preoperative sodium depletion has not been excluded in these patients.

## VII. Conclusion

From this review of body fluid disturbances in surgical patients it should be apparent that the same common denominators are present on surgical wards as well as on medical and pediatric services. The problems facing the surgeon, however, are often more urgent and more frequent than those facing his medical colleagues. For this reason much of our knowledge of both the practical and the theoretical aspects of body fluid therapy has come from investigations of surgical patients. The understanding and the intelligent management of these problems, however, know no departmental boundaries.

**SUMMARY:** It is now recognized that slight increases in body temperature and pulse rate, decreases in urine volume and body weight, retention of sodium, and increased excretion of potassium and nitrogen represent metabolic effects of uncomplicated surgery. These manifestations are self-limited. They may be altered or require therapeutic attention in patients undergoing protracted pre-surgical or post surgical courses with gastrointestinal fluid losses, circulatory and renal problems, etc. The fundamental principles of fluid therapy in these and other types of surgical patients can be reduced to simple terms, defining volume and composition of the replacement solutions in accordance with well-established physiologic limitations. These apply even in some of the newer developments in surgery such as adrenalectomy, hypophysectomy, and cardiac surgery.

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PART IV

*Clinical Dicta and Practical Therapeutics*





“ . . . there is no separate science of medicine or physiology, there is only a science of life.”

Claude Bernard in *An Introduction to the Study of Experimental Medicine*

## Chapter 22

### CLINICAL AND LABORATORY ASSESSMENT OF BODY FLUID DISTURBANCES

To apply the principles of body fluid physiology presented in Parts I and II to the care of sick patients in general as well as those ill with one or another of the disease entitites discussed in Part III, the physician requires certain practical knowledge and skills. These include a working knowledge of the clinical and laboratory methods of diagnosis, an ability to assess the specific requirements of fluid therapy, and a familiarity with the technics necessary to implement that therapy.

#### I. The Basic Approach to the Problem

In treating the disturbed body fluids of a sick patient the physician goes through four essential steps. 1) When first confronted with the problem he makes the best tentative diagnosis possible from the history and physical examination of the patient (e.g., vomiting, diarrhea, hypotension suggest a deficit of extracellular fluid). 2) If the tentative diagnosis is sufficiently specific, he applies his knowledge of the pathological physiology of that particular condition (e.g., diabetic ketosis is almost always accompanied by deficit of extracellular sodium and water, relative excess of ketone acids, and deficit of intracellular potassium). 3) Then and then only does he turn to the laboratory for biochemical aid in making the diagnosis. Usually such aid consists of determining the concentrations of various body fluid constituents in blood or serum. If so, these measurements furnish only indirect clues to changes in other dimensions and in other portions of the body fluids, and so must be interpreted. 4) In light of the three foregoing steps the physician then makes the best estimate of the patient's requirements, administers fluids as judgment dictates and observes the result. Having assessed the result he then modifies his future therapy accordingly. All intelligent fluid therapy is really a matter of *trial and error*. This is

TABLE 22-I.

SUMMARY OF DIAGNOSTIC EVIDENCE INDICATING ABNORMALITIES OF BODY FLUID CONSTITUENTS:				WATER AND SODIUM
PRIMARY FLUID DISTURBANCE	HISTORY	CLINICAL SIGNS AND SYMPTOMS	BIOCHEMICAL SIGNS	
WATER				
A. Dehydration	Fluid restriction, diabetes insipidus	Thirst, weight loss, oliguria, dryness of mucous membranes, fever, loss of skin turgor, low urine volumes	Hypernatremia Hemoconcentration	
B. Overhydration	Excessive administration salt-free fluids during renal failure	Edema, restlessness, twitching, muscle cramps, convulsions, coma	Hyponatremia	
SODIUM (and chloride)				
A. Deficit	Gastro-intestinal fluid loss, diabetic ketosis, adrenal insufficiency, excessive mercurial diuresis on low-sodium diet	Peripheral vascular collapse hypotension, tachycardia, oliguria, paralytic ileus	Azotemia Hyponatremia (+)	
B. Excess	Local venous obstruction, congestive heart failure, cirrhosis, nephrosis, acute glomerulonephritis, ACTH, cortisone, premenstrual	Edema, peripheral or pulmonary	Iso-, hyper-, or hyponatremia	



so even though absolute measurements may be made of the volume of specific portions of the body fluids and changes in ionic content may be calculated from these and the associated concentration values. Since intracellular concentrations are not readily sampled, exchanges between cells and extracellular fluid are difficult to predict quantitatively, and future concomitant exchanges with the environment can only be roughly estimated. Thus the precise amount of water to restore urine flow in dehydration, the precise amount of blood to restore the blood pressure after hemorrhage, the exact amount of sodium lactate or sodium bicarbonate to restore the blood pH or buffer base concentration to normal in metabolic acidosis, or the precise amount of potassium to reconstitute a deficit of intracellular potassium, are all a matter of therapeutic trial. Knowledge, judgment and experience enter into the making of the best estimate possible from the evidence at hand (1a-p).

#### *A. De Novo and Day by Day Assessment*

The patient first seen obviously presents a different problem in assessment of fluid requirements from the patient who has been under observation in the hospital from day to day. In the latter case some quantitative information should be available concerning prior fluid intake, prior fluid output, and clinical manifestations of body fluid abnormalities. Routine measurements of total intake and output of fluid are well-known to be subject to error, but are nevertheless extremely helpful in guiding therapy. The daily change in weight, if known, is of the greatest value and trends in serum electrolyte concentrations usually yield more information than single determinations.

## **II. Diagnosis of Specific Abnormalities of Certain Fluid Constituents**

#### *A. Water (Table 22-I)*

The principal symptom of deficit of water or *dehydration* is thirst—if the patient is sufficiently conscious and able to indicate it. The major signs are oliguria and rapid weight loss. Dryness of the mucus membranes, loss of skin turgor (where there is no other reason for diminished elasticity such as age), and fever, are suggestive but not pathognomonic signs. Biochemical signs are those indicating loss of water relative to solutes in the body fluids: elevated relative red cell volume (hematocrit value) and hemoglobin concentration, elevated serum sodium concentration or hyponatremia (2a-e). This important sign of hyponatremia is absent only if there has been a loss of electrolyte concomitant with the loss of water. The best evidence of the existence of pure dehydration is the restoration of urinary volume following administration of several extra liters of electrolyte-free

solutions (water by mouth, five or ten per cent glucose solutions by vein). Such a therapeutic test should be tried with caution in patients in shock or in whom severe intrinsic renal damage is suspected.

Excess of water or *overhydration* without accompanying retention of electrolyte almost always is associated with excessive administration of salt-free solutions during renal shutdown. Clinically it is manifested by restlessness, apprehension, muscular twitching, muscle cramps, or the convulsions of water intoxication (3a-c). Edema may be present and the cardinal biochemical sign is hyponatremia.

### *B. Sodium and Chloride (Table 22-I)*

Deficits of sodium are usually accompanied by deficits of other extracellular ions, especially chloride, and of extracellular water. History of any condition associated with the renal loss of sodium (diabetic acidosis, adrenal insufficiency, chronic glomerulonephritis, excessive mercurial diuresis with low sodium diet) or of any abnormal loss of gastrointestinal fluids (vomiting, diarrhea, fistulae, gastrointestinal suction) should immediately raise a strong suspicion of deficit of sodium and extracellular fluid. The clinical signs are primarily those of peripheral vascular collapse: rapid and thready pulse, hypotension, cold and clammy extremities, cyanosis and severe oliguria. Biochemical signs are primarily those indicating diminished plasma volume or hemoconcentration; rising hematocrit and hemoglobin concentration and evidence of progressive renal failure; rising concentration of urea or nonprotein nitrogen, creatinine, phosphate, and other undetermined anions in blood or serum, falling total serum content of carbon dioxide (2a, 4a-g). The serum sodium concentration may be low, and if so, is diagnostically helpful, but it is not necessarily low if the loss of water has paralleled that of sodium. Reversal of the above clinical and biochemical signs with the administration of a solution which contains sodium is confirmatory evidence.

Except in association with certain intracranial lesions leading to hyponatremia (see chapter 19) *excess* of sodium is almost always accompanied by an excess of water. The cardinal sign is edema, peripheral or pulmonary. Edema may be due to local venous obstruction or to systemic diseases such as congestive heart failure, cirrhosis, nephrosis, nephritis, or the nephrotic syndrome and exogenous or endogenous excess of adrenal and gonadal steroids. Edema seldom results from a high intake of sodium unless one of these other conditions is present. Biochemical signs are not helpful; the serum sodium concentration is usually unchanged but may be elevated or depressed according to the simultaneous transfers of water.

### C. Bicarbonate and Anion-Cation Balance (Table 22-II)

The ratio of the concentration of carbonic acid to that of bicarbonate and other buffer anions (summed as "buffer base") determines the pH of blood and extracellular fluid. Since the former is regulated by gas exchange in the lungs and the latter by metabolic or renal transfers, abnormalities in this system may be primarily *respiratory* or primarily *metabolic*. Secondary or compensatory changes may occur in the other half of the system sometimes to such a degree that determination of which change is primary can only be made from clinical evidence and not from biochemical findings. These clinical disturbances of this system have already been discussed in detail in chapters 10 and 11 and are summarized in table 22-II.

### D. Potassium (Table 22-III)

*Deficiency* of this intracellular ion must be suspected primarily from the clinical circumstances (5a). These are especially the association of absence of intake (no cellular food) with stress (postoperative, trauma, infection) and other causes of hyperadrenocortical activity (DOCA, ACTH, cortisone, Cushing's disease). Abnormal losses of the ion may occur in urine and in gastrointestinal fluids. The former occurs during the polyuric phase of acute renal failure though so-called potassium wasting forms of chronic nephritis have been described (5b, c). Clinical signs and symptoms are usually not very specific: weakness, mental confusion, diminished deep reflexes, and occasionally muscular paralysis (especially accessory respiratory muscles). Paralytic ileus can occur (5c, d). Electrocardiographic signs are suggestive, if present, and increased sensitivity to digitalis may be apparent. Biochemical signs are indirect: the most useful is the finding of a low concentration of potassium in serum (hypokalemia) and extracellular fluid which almost always indicates intracellular deficit (except after insulin, epinephrine, glucose or when anabolic agents such as testosterone have been administered) or in the disease familial periodic paralysis.

Intracellular deficits may also be present when the serum concentrations of potassium are elevated, as in the early stages of diabetic coma and infant diarrhea, but these fall to low levels on the administration of fluid and the improvement of renal function (5c, f).

Metabolic alkalosis with high total serum carbon dioxide content may be associated with intracellular potassium deficit (figs. 3-15, 3-16 and 22-1). A very low concentration of potassium in urine, four to two milliequivalents per liter, or a urine/plasma ratio in the vicinity of unity is occasionally observed in patients with good renal function who have sustained a potassium deficient state over many days (5g, h). Abnormal renal loss or wasting of potassium, on the other hand, is difficult to establish unless the



TABLE 22-II.

DIAGNOSTIC EVIDENCE INDICATING SPECIFIC ABNORMALITIES: BICARBONATE-ACID : BASE			
PRIMARY FLUID DISTURBANCE	HISTORY	CLINICAL SIGNS AND SYMPTOMS	BIOCHEMICAL SIGNS
BICARBONATE-ACID: BASE BALANCE			
A. Metabolic acidosis	Renal disease, diabetes mel- litus, exogenous acids (boric, salicylic, etc), diarrhea	Hyperpnea without tetany stupor, convulsions,	Low total serum $\text{CO}_2$ , low blood buffer base and pH, high serum chloride or undetermined anion, acid urine
B. Metabolic alkalosis	Excess alkali, vomiting or gastric suction, K deple- tion with stress, administration ACTH, DOCA, or cortisone, Cushing's disease, mercurial	Hypopnea, tetany, confusion	High total serum $\text{CO}_2$ , high buffer base and pH, low serum chloride, serum K (+), alkaline or acid urine
C. Respiratory acidosis	Chronic pulmonary insuf- ficiency, unconsciousness with $\text{O}_2$ therapy	Fixed large chest, difficulty with expiration, dyspnea, cyanosis	High $\text{PCO}_2$ and total $\text{CO}_2$ content of serum, low pH and low serum chloride, acid urine
D. Respiratory alkalosis	Emotional hyperventilation, encephalitis, intracranial lesion or operation	Tetany, hyperventilation (+)	Low $\text{PCO}_2$ and total $\text{CO}_2$ content of serum, high pH, occas. high serum chloride, alkaline urine

TABLE 22-III.

SUMMARY OF DIAGNOSTIC EVIDENCE INDICATING SPECIFIC ABNORMALITIES OF BODY FLUID CONSTITUENTS: POTASSIUM			
PRIMARY FLUID DISTURBANCE	HISTORY	CLINICAL SIGNS AND SYMPTOMS	BIOCHEMICAL SIGNS
POTASSIUM A. Deficit	Low K intake during stress, DOCA, ACTH, or cortisone therapy, polyuric phase of acute renal failure, diabetic ketosis	Weakness, mental confusion, diminished deep reflexes, muscular paralysis, paralytic ileus, sensitivity to digitalis, ECG changes	Hypokalemia usually but not always, high total CO <sub>2</sub> and pH (+), K in urine approaching U/P ratio of 1.0 occas.
	B. Excess	Renal insufficiency (usually with oliguria), overdosage of K, adrenocortical insufficiency	Hyperkalemia, except in early diabetic coma and infant diarrhea when cells are deficient

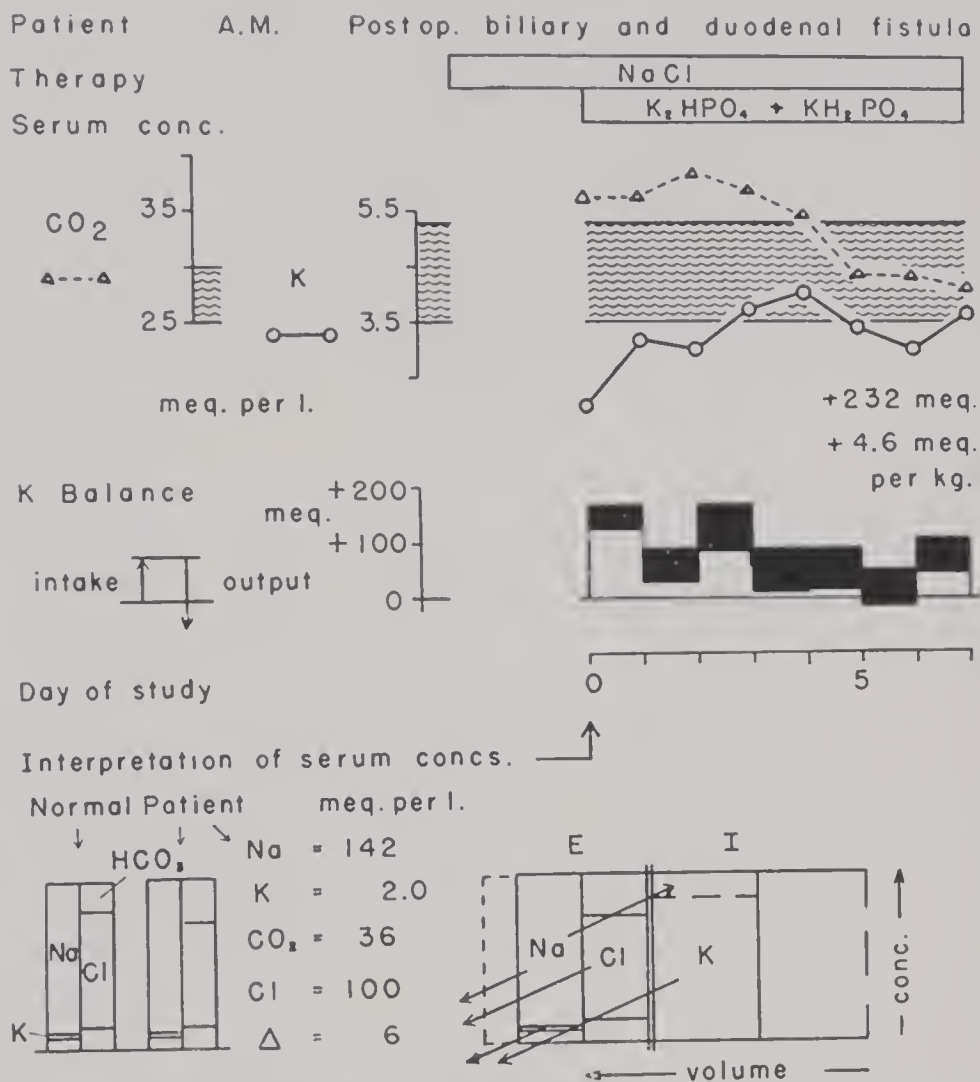


FIG. 22-1. ELECTROLYTE AND WATER CHANGES WITH LOSSES OF GASTROINTESTINAL SECRETIONS. SERUM CONCENTRATION: LOW POTASSIUM, HIGH CARBON DIOXIDE

Clinical data and diagnosis. A. M., a 63-year-old white male with postoperative biliary and duodenal fistula following choledochoduodenostomy for biliary carcinoma was maintained on potassium-free parenteral fluids up to day one. Intravenous administration of buffered potassium phosphate solution resulted in positive potassium balance. The patient recovered.

Interpretation of serum concentration at start of day one: *Body fluid pattern*: Diminution of extracellular sodium and water volume without significant change in sodium concentration, excess of bicarbonate; deficit of extracellular and intracellular potassium with excess of intracellular sodium.

*Physiologic mechanism*: Loss of sodium and chloride in fluids lost through fistula; potassium deficit resulted when potassium was excreted in urine and in fistula fluid during period of potassium-free intake. (From Squires and Elkinton (1a).)

exact balance, intake as well as output, has been measured over a prolonged period.

*Excess of potassium in extracellular fluid* in terms of concentrations is of great clinical import because of its toxic effect on the heart. It occurs most commonly in patients with renal insufficiency who are usually but not



always oliguric, or in patients with limited renal function who have received an overdose of the ion (6a). Hyperkalemia is characteristic of adrenocortical insufficiency. Excess of intracellular potassium is probably present in this latter state (6b) and can occur at least temporarily as the result of excessive administration of the ion, but its functional effect, if any, is not known. The clinical signs and symptoms of excess of potassium are not definitive: paresthesias and even paralysis have been described (5c). Electrocardiographic evidence of increased sensitivity of the heart (elevated T waves, conduction defects, extrasystoles) are somewhat better defined and may be diagnostic (6c) (See fig. 9-8). The biochemical sign is hyperkalemia.

As mentioned earlier, hyperkalemia may also be present with cellular deficits during the early stages of diabetic coma and acute infant diarrhea but disappears when fluid administration restores renal function.

#### *E. Phosphorus (Table 22-IV)*

The phosphorus of the body is present in inorganic and in organic forms. Serum or plasma and the interstitial fluid contain only inorganic phosphorus. Its level varies with age (see chapter 4) and with transfers into or out of cells. Thus glycolysis or glycogenesis induced by glucose or insulin administration lowers the concentration; diabetic coma raises it (7a-d).

*Deficit* of body phosphorus as a whole may result from a low intake of cellular foods (no meat, vegetable or milk), poor absorption from the gut (lack of vitamin D, presence of steatorrhea), increased renal excretion (primary and secondary hyperparathyroidism), and breakdown of cellular phosphorylation (diabetic ketosis). There are no specific clinical signs and symptoms other than those associated with the underlying disease process. Biochemical evidence is a diminished concentration of inorganic phosphorus in serum and extracellular fluid.

*Excess* of body phosphorus may occur with a high intake by a patient with a mild impairment of renal function, and almost always occurs in any patient with far-advanced renal insufficiency but hypoparathyroidism is also a cause (7a, e). The prime clinical manifestation is tetany due to the hypocalcemia which frequently ensues. Biochemical evidence is hyperphosphatemia with more or less hypocalcemia; renal insufficiency is indicated by azotemia (elevated urea or nonprotein nitrogen), high serum creatinine, high undetermined anion, and low total carbon dioxide and pH.

#### *F. Calcium (Table 22-IV)*

Abnormal distributions of calcium in the body fluids are less readily categorized as deficits or excesses since one condition may obtain in bone, the principal depot of calcium in the body, and the other in extracellular fluid because of differential rates of entry and egress (7a). In addition, in

TABLE 22-IV.

SUMMARY OF DIAGNOSTIC EVIDENCE INDICATING ABNORMALITIES OF BODY FLUID CONSTITUENTS: PHOSPHATE AND CALCIUM			
PRIMARY FLUID DISTURBANCE	HISTORY	CLINICAL SIGNS AND SYMPTOMS	BIOCHEMICAL SIGNS
<b>PHOSPHATE</b>			
A. Deficit	Low intake, primary and secondary hyperparathyroidism, diabetic ketosis	None	Hypophosphatemia
B. Excess	High intake, hypoparathy., renal insufficiency	Tetany	Hyperphosphatemia, hypocalcemia, low total CO <sub>2</sub> and pH, high "undetermined anion" in serum
<b>CALCIUM</b>			
A. Deficit	Lack of Vitamin D (rickets), steatorrhea, hypoparathyroidism, or (hyperparathyroidism, metastatic carcinoma, sarcoid, disuse, menopause, renal tubular acidosis)*	Tetany, (bone pain fractures, x-ray osteoporosis, osteitis fibrosa cystica, osteomalacia, renal stones)*	Hypocalcemia, or (hypercalcemia and hypercalcuria on low Ca intake)*
B. Excess	Excessive Vitamin D intake, high Ca intake	X-ray osteoplastic lesions, calcification in soft tissues, renal stones and insufficiency	Hypercalcemia

\* Deficit in bones but excess in extracellular fluid

any individual clinical situation the relationship of the actual calcium level to the concentrations of phosphorus and of albumin must be kept in mind (8a, b). Also, the proportion of calcium present in ionized form and the effects of pH on the degree of ionization should be considered (8c) even though such fractionation is not readily accomplished in most clinical laboratories.

*Deficit* in both extracellular fluid and bone is found in rickets due to lack of vitamin D, in steatorrhea causing inadequate absorption, in low intake in relation to utilization, as in pregnancy, and in hypoparathyroidism (7a). These conditions are characterized clinically by tetany and biochemically by hypocalcemia and hypocalciuria. In an earlier chapter it was pointed out that hypocalcemia may mask the clinical and electrocardiographic manifestations of potassium deficiency and that conversely tetany does not appear in such patients until the potassium has been replaced (8d).

Localized or generalized deficits may occur in bone while the ion is in excess in extracellular fluid, due to its mobilization and transport. This occurs in hyperparathyroidism, malignant tumors metastatic to bone, sarcoid, multiple myeloma, osteoporosis due to disuse or the menopause, and in renal tubular acidosis. The clinical signs and symptoms include bone pain, fractures, x-ray osteoporosis, osteofibrosis cystica, osteomalacia, and renal calcinosis. In these conditions there is hypercalcemia and hypercalciuria on a low calcium intake (7a, 8a-m).

*Excess* of calcium in fluids and in bone may result from high intake of vitamin D (50,000 to 1,000,000 or more units per day) and of calcium, over prolonged periods (8n-p). With the larger amounts of vitamin D bone destruction and loss of bone calcium occurs. A similar excess may develop with continued alkali-milk regimens of the type used in treating peptic ulcers. With this as with the other forms of hypercalcemia corneal calcification may develop (8q, r).

#### *G. Magnesium (Table 22-V)*

Although magnesium is quantitatively a major intracellular cation and is known to have important pharmacological effects in the central nervous system, the neuromuscular junction, and the heart (9a-e), relatively little is known of its pathological distribution in disease states.

*Deficits* have been reported due to low intake in patients on magnesium-free parenteral fluids and to excessive renal loss in patients with acute renal failure in the polyuric phase, with chronic renal insufficiency, and during mercurial diuresis (9f-h). The signs and symptoms are not well defined although anorexia, vasodilation, neuromuscular hyperirritability, convulsions, and tetany may be associated and in the rat decreased protein synthesis and kidney damage have been demonstrated (9i-n). The biochemical



TABLE 22-V

SUMMARY OF DIAGNOSTIC EVIDENCE INDICATING ABNORMALITIES OF BODY FLUID CONSTITUENTS: MAGNESIUM			
PRIMARY FLUID DISTURBANCE	HISTORY	CLINICAL SIGNS AND SYMPTOMS	BIOCHEMICAL SIGNS
MAGNESIUM A. Deficit	Low intake (Mg. free fluids post-operative) acute or chronic renal disease with polyuria, Hg. diuresis	Neuro-muscular hyper-irritability, ? tetany, ? anorexia	Hypomagnesemia
B. Excess	High intake, renal insufficiency with oliguria	Neuro-muscular, central nervous system and cardiac depression	Hypermagnesemia

sign is a low concentration of magnesium in serum (hypomagnesemia) but it is probable that, as in the case of potassium, an elevated extracellular concentration may coexist with a cellular deficit under conditions of dehydration, renal insufficiency, and accelerated cellular transfers (9o).

*Excess* of magnesium, again like potassium, is usually found in patients with severe renal insufficiency and oliguria. This is most likely if the patient is receiving magnesium salts, such as magnesium sulfate (Epsom salts) or even magnesium hydroxide (milk of magnesia). The clinical signs are those of depression of the central nervous system (drowsiness) and of the neuromuscular function (diminished or absent deep reflexes, weakness) or, as with deficits, peripheral vasodilation (9p-t). Hypermagnesemia is present.

The state of magnesium with regard to its ionization or, more precisely, its ultrafiltrability in these various disease entities has not been defined. In thyroid diseases however the ultrafiltrable portion has been found altered. This is discussed in chapter 17.

**SUMMARY:** A tentative diagnosis of the patient's illness and a knowledge of the types of body fluid disturbances that occur in that particular entity are indispensable preliminaries to intelligent requisitioning and use of biochemical analyses. Knowledge of the possible independent, as well as the related, variations of concentrations and total amounts of electrolytes is necessary in the interpretation of the significance of sodium, potassium, calcium, magnesium, chloride, bicarbonate and phosphorus values in serum.

Actual therapy thereafter is based upon the application of the known parameters relating to deficits or excesses and the boundaries within which manipulation of the body fluids is safe. The effectiveness of the therapy is then assessed by serial biochemical analyses and the clinical course of the patient.

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## *Chapter 23*

### **RANGE OF REQUIREMENT OF INDIVIDUAL FLUID CONSTITUENTS AND THEIR HOMEOSTATIC LIMITATIONS**

In the preceding chapter the clinical and laboratory assessment of body fluid disturbances has been discussed in terms of individual components. In this chapter the water and the individual solutes will be discussed in terms of the orders of magnitude involved in impending or existing deficits, or excesses. Throughout, it must be remembered that the various constituents condition each other in their effects in the body. This is especially true in respect to total water and total solute and the rate of administration of one must always be considered in relation to that of the others. The reader is also to be reminded again that all fluid therapy is a matter of trial and error. Therapeutic effects must be carefully observed and future therapy modified accordingly.

#### **I. Water**

The daily net turnover of water ranges between three and six per cent of the total body water (Table 23-I) (1a-c). Balance is maintained if the intake of water meets the two basic needs of losing body heat by vaporization through lungs and skin and excreting solutes through the kidneys. In addition any abnormal loss of water from the gastrointestinal tract must be replaced.

##### *A. Water of Vaporization or Insensible Water Loss*

This amounts to 800 to 1500 ml. per day in the nonfebrile resting adult and average about 600 ml. per square meter of body surface per day (1f-h). When the patient becomes febrile and sweating ensues the extrarenal water loss may increase by 1000 to 2000 ml. per day. The minimum and maximum water requirements for heat loss, therefore, approximate respectively 500

TABLE 23-1

RANGE OF NORMAL DAILY NET TURNOVER AND APPROXIMATE BODY CONTENT OF PRINCIPAL CONSTITUENTS OF THE BODY FLUIDS									
Constituent	Unit	Daily turnover (intake-output)		BODY CONTENT*			Total	Turnover total content (%)	References
				"Extracellular" "Intracellular"					
Water	l./adult <sup>#</sup> l./M <sup>2</sup> sf.area ml/kgm.wt.	1.5 - 3.0 8.70- 17.30 21 43	12 - 15 6.9- 8.7 172 - 214	28 - 31 16 - 18 400 - 443	40- 46 23- 27 570- 660	3 - 6			1a-e
Sodium	mEq/adult <sup>#</sup> mEq/M <sup>2</sup> sf.area mEq/kgm.wt.	85 -250 49 -145 1.2 - 3.6	1700 -2100 980 -1210 24 - 30	900 -1100 520 - 640 13 - 16	2700-3000 <sup>§</sup> 1560-1730 39- 43	3 - 9			5a-f
Chloride	mEq/adult <sup>#</sup> mEq/M <sup>2</sup> sf.area mEq/kgm.wt.	85 -250 49 -145 1.2 - 3.6	1400 -1750 800 -1000 20 - 25	500 - 650 290 - 370 7 - 9	1900-2400 1100-1400 27- 32	3.5-13			8f, g
Potassium	mEq/adult <sup>#</sup> mEq/M <sup>2</sup> sf.area mEq/kgm.wt.	50 - 150 29 - 88 0.7 - 2.1	48 - 60 28 - 35 0.7- 0.9	2950 -3350 1700 -1930 42 - 48	3000-3400 <sup>†</sup> 1730-1960 43- 49	1.5- 5			9a-d
Magnesium	mEq/adult <sup>#</sup> mEq/M <sup>2</sup> sf.area mEq/kgm.wt.	20 - 50 12 - 29 0.3 - 0.7	24 - 30 14 - 17 0.3- 0.4	810 -1170 470 - 530 12 - 17	840-1200 490- 690 12- 17	1.3- 3.6			1b 11a-c
Carbon dioxide	mM/adult mM/M <sup>2</sup> sf.area mM/kgm.wt.	13000 <sup>**</sup> 7500 186	380 - 480 190 - 280 5.4- 6.9	340 - 370 195 - 225 4.9- 5.3	720- 850 415- 490 10- 12	1500-1800			12a, b

- \* Approximated from data obtained by whole body analyses, tissue analyses, and isotope dilution in intact man. "Extracellular" is taken to include the connective tissue subphase; "Intracellular" is simply the difference between this approximate "extracellular" phase and the total for the body.
- <sup>#</sup> Average adult taken to be male of normal habitus, 70 kgm. body weight, and surface area of 1.73 M<sup>2</sup>.
- <sup>§</sup> Calculated from "exchangeable" sodium; much of the intracellular sodium is in the skeleton; non-exchangeable sodium may increase the total body content to about 5600 mEq or 80 mEq/kgm (1b).
- <sup>†</sup> Calculated as "exchangeable" potassium.
- \*\* Calculated from a basal metabolic rate of CO<sub>2</sub> production of 200 ml. per min.



and 2000 ml. per square meter per day or 12 and 50 ml. per kg. per day, i.e., 800 and 3500 ml. per day in a 70-kg. adult.

### *B. Urinary Water*

Water required for excretion of solutes depends upon these factors: *a*) the rate of endogenous catabolism presenting nonprotein nitrogen, creatine and creatinine, organic acids, potassium, and phosphate for excretion, *b*) the need for excretion of simultaneously administered or injected solutes, and *c*) the concentrating ability of the kidney. Many investigators have studied the quantitative relationships between renal solute excretion and renal water excretion (2a-e). For practical purposes these quantitative relationships may be summed up as follows. Factor (*a*) approximates 200 milliosmols per square meter per day or five milliosmols per kg. per day, i.e. 350 milliosmols per day in a 70-kg. adult. Factor (*b*) is difficult to predict because of uncertainty as to retention or metabolism of administered exogenous solute. A rule of thumb is to allow for one-half the milliosmolar content of the infused solution. Factor (*c*) has been found to lie between 0.7 ml. per milliosmol in the normal to 2.5 ml. per milliosmol in the stressed patient. Under the need to conserve water, therefore, the sick patient of 70-kg. weight may require a minimum of as much as 900 ml. per day (500 ml. per square meter per day or 13 ml. per kg. per day). A maximum limit on water excretion is determined by the ability of the kidney to dilute urine in relation to solute content. The limit of this factor is about 10 ml. per milliosmol. Therefore, under the need to excrete water when only endogenous solutes are available, the maximum urinary water excretion is about 3500 ml. per day for the average 70-kg. adult (2000 ml. per square meter per day or 50 ml. per kg. per day). This maximum is rapidly increased when more exogenous solute is available. These minimum and maximum relationships, as correlated and presented graphically by Talbot, Crawford, and Butler (2f), are shown in figure 23-1.

### *C. Balances of Body Water*

Practically, maintenance of daily water balance in an average 70-kg. adult may be summed up as follows:

Give:	1000-1200 milliliters for insensible vaporization
	800-1000 milliliters for urine
	<hr/>
	1800-2200 total
Add:	500-1500 for fever and sweating
	Equivalent volumes with salt for abnormal losses of gastrointestinal fluid
	Any estimated water deficits (see below)
Subtract:	Water for urine in anuria due to acute renal failure

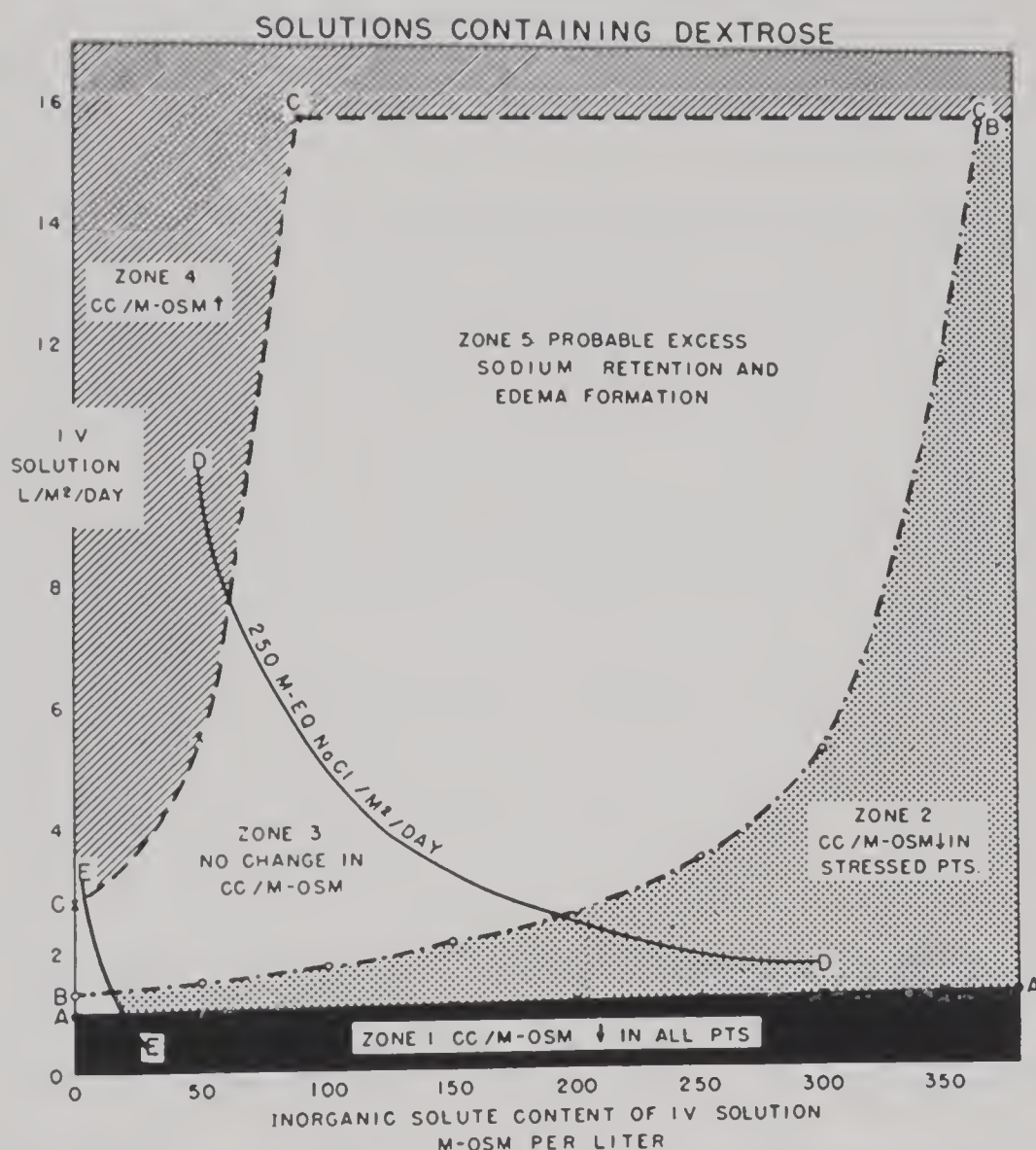


FIG. 23-1. MINIMAL AND MAXIMAL PARAMETERS OF REQUIREMENTS AND TOLERANCE FOR WATER AND SOLUTES AS DEFINED BY TALBOT ET AL. (2f)

The effect on body water is shown of infusing dextrose solutions containing sodium chloride in concentration from 0 to 350 mOsm. per liter. The ordinate indicates the rate of fluid infusion expressed in liters per square meter per day; the abscissa indicates the sodium chloride content in mOsm. per liter. The theoretical effects of administration of various amounts of fluids containing varying salt content upon the recipient's body water concentrations expressed as cc. per mOsm. of total solute are suggested by the zones defined by curves A to E.

Curve A-A shows the minimum water requirement of a patient not under stress. Failure to meet this requirement places him in Zone 1 where he must expend his own endogenous water and becomes dehydrated. Curve B-B shows the minimum water requirement of a patient under stress who is less able to concentrate his urine; more water is needed to keep him out of Zone 2 where he must supplement with his own endogenous water. Maximum water tolerance is shown by Curve C-C; patients in Zone 3 develop overhydration and water intoxication.

Curves D-D and E-E define minimum and maximum sodium chloride tolerances; patients in Zone 5 will develop edema. This leaves Zone 4, defined by Curves B to E inclusive, as the safe zone in which no change in body water concentration will be induced.

The source of the water so given may be by ingestion, parenteral administration, or from water of oxidation and catabolism, (up to 450-500 milliliters per day).

**1. Deficits** of water in the dehydrated patient may be severe, amounting to six to 10 per cent of the total body water (tables 23-II, 23-V) (3a-c). This is four to seven liters in the average adult. Less severe degrees of dehydration, more commonly encountered, amount to one to three liters per adult. Where the data are available, deficits may be calculated approximately as follows:

- (a) as equivalent to acute weight loss (if previous weight is known)

Example:

$$\text{Initial wt.} = 70.0 \text{ kg.}$$

$$\text{Final wt.} = 66.8 \text{ kg.}$$

$$\text{Difference} = 3.2 \text{ kg.} \approx 3.2 \text{ liters H}_2\text{O}$$

- (b) as equivalent to urine and gastrointestinal fluid plus estimated insensible water observed and estimated to have been lost since prior state of normal hydration, minus intake of water

Example (during 2 days):

$$\text{Output: urine} = 900 \text{ ml.}$$

$$\text{H}_2\text{O vaporization} = 3000$$

$$\text{Gastric fluid} = 2800$$

$$\text{Total} = 6700 \text{ ml.}$$

$$\text{Intake: oral fluids} = 400$$

$$\text{i.v. fluids} = 4000$$

$$\text{H}_2\text{O oxidation} = 200$$

$$\text{Total} = 4600$$

$$\text{Balance H}_2\text{O} = -2.1 \text{ liters}$$

- (c) from the rise in serum sodium concentration and the estimated normal total body water,  $W_1$ , provided there has been no significant electrolyte loss or gain, as in water deprivation or diabetes insipidus:

$$\text{Deficit H}_2\text{O} = W_1 - W_2$$

$$= (0.6 \text{ Wt.}) - \frac{\text{Na}_{s_1} \times (0.6 \text{ Wt.})}{\text{Na}_{s_2}}$$

Example:

$$\text{Given: Wt.}_1 = 70 \text{ kg.}$$

$$\text{Na}_{s_1} = 140 \text{ mEq./l}$$

$$\text{Na}_{s_2} = 160 \text{ mEq./l}$$

$$\text{Then } W_1 = 0.6 \times 70 = 42 \text{ liters}$$

$$W_2 = \frac{140 \times 42}{160} = 37 \text{ liters}$$

$$\text{Deficit H}_2\text{O} = 42 - 37 = 5 \text{ liters}$$



TABLE 23-II  
OBSERVED AND CALCULATED DEFICITS\* OF CERTAIN BODY FLUID CONSTITUENTS IN VARIOUS CLINICAL CONDITIONS  
Expressed in units per kilogram of body weight

CONDITION	INVESTIGATORS	TYPE OF STUDY#	NO. OF PTS.	WATER			CHLORIDE		
				mean	TOTAL max.	min.	mean	TOTAL max.	min.
					milliliters/kilogram	EXTRACELLULAR <sup>+</sup> mean	meq./kilogram		
Diabetic acidosis	Atchley et al. (3a)	bal.-	2	89	( 92	85)	2.5	( 3.0	1.9)
	Butler et al. (7a)	bal.-	1			110	4.0		
	Danowski et al. (7b)	bal.+	8			76 (208	9.5	(26.2	1.1)
	Darrow, Pratt (3b)	bal.+	1	114		80	9.0		
	Nabarro et al. (3c)	bal.+	7	87	( 92	44)	5.1	(10.0	3.1)
Gastro-intestinal fluid loss starvation	Darrow (7c)!!	bal.+	6				14.8	(28.8	2.1)
	Tarail, Elkinton (7d)	bal.+	4			14	4.4	( 9.3	- 1.5)
	Darrow et al. (7e)!!	bal.+	8			125 (202	9.2	(29.0	2.1)
	Danowski et al. (7f)§	bal.+	4			268 (438	39.5	(54.3	13.2)
	Elkinton et al. (7g)	bal.+	4			49 ( 93			
	Schwartz, Relman (8a)	bal.+	2						
	Eliel et al. (8b)!	dil.-	1			26			
	Mudge, Vislocki (3d)	tis.-	3	2	( 4	0)	3.6	( 5.7	1.6)
Adrenocortical insufficiency	Harrop et al. (12c)\$								
	Elkinton (3e)	bal.+	1	23		123	2.1		
	Hills et al. (12d)			4	( 17	- 7)	16.5	( 4.1	- 0.6)
Postop. 5 days Burns	Moore et al. (8c)*	bal.-	75						
	Moore et al. (8d)	bal.-							
Renal tubular acidosis	Elkinton et al. (7h)	bal.+	1			2	- 1.6		
	Pines, Mudge (7i)	bal.+	2			20 ( 38	0	( 2.0	- 2.0)
	Elkinton et al. (7j)	bal.+	3			3 ( 48	0.1	( 3.3	- 2.2)
Uremic acidosis	Iseri et al. (4a)	bal.+	6	-123	(- 22	-206)	- 9.2	(-0.1	-18.7)
	Stock et al. (4b)	bal.+	4	-142	(- 66	-259)	-18.1	(-8.6	-29.7)
	Squires et al. (4c)	bal.+	5	-217	(-129	-384)	-14.2	(-8.5	-21.6)
	Hurst et al. (4d)	dil.+	20	-123	(- 10	-294)			
	Warner et al. (8e)**	dil.	14			-109			
	Talso et al. (4e)	tis.	8	-123	(-100	-154)	- 2.5	( 1.2	- 5.7)

See footnotes to Table 23-IV

TABLE 23-III

OBSERVED AND CALCULATED DEFICITS\* OF CERTAIN BODY FLUID CONSTITUENTS IN VARIOUS CLINICAL CONDITIONS

CONDITION	INVESTIGATORS	TYPE OF STUDY#	NO. OF PTS.	SODIUM			INTRACELLULAR <sup>⊗</sup>	
				mean	TOTAL max. min. milliequivalents/kilogram	mean	max.	min.
Diabetic acidosis	Atchley et al. (3a)	bal. -	2	5.9	( 6.7 5.1)			
	Butler et al. (7a)	bal. -	1	5.1				
	Danowski et al. (7b)	bal. +	8	10.4	( 25.2 4.9)	- 1.7	( 2.2	- 7.5)
	Darrow, Pratt (3b)	bal. +	1	13.3				
	Nabarro et al. (3c)	bal. +	7	7.2	( 9.6 5.5)	1.4		
Gastro-intestinal fluid loss and starvation	Darrow (7c)!!	bal. +	6	16.6	( 29.1 5.7)			
	Tarail, Elkinton (7d)	bal. +	4	7.3	( 15.0 1.9)	- 3.1	( 2.4	- 6.8)
	Darrow et al. (7e)!!	bal. +	8	9.5	( 29.3 - 2.1)	- 3.3	( 3.7	- 9.5)
	Danowski et al. (7f)Ω	bal. +	4	25.3	( 32.5 5.8)	- 18.2	(- 4.9	- 24.5)
	Elkinton et al. (7g)	bal. +	4	0	( 11.3 - 11.6)	- 9.3	( 14.2	0 )
	Schwartz, Reiman (8a)	bal. +	2	- 22.6		10.8	(- 10.8	- 10.8)
	Eliel et al. (8b)♠	bal. -	1	- 4.7	(- 0.6 - 12.2)	- 19.7	(- 1.1	- 16.0)
	Mudge, Vislocki (3d)	tis. -	3	2.5		- 7.2		
	Harrop et al. (12c)§							
	Elkinton (3e)	bal. +			( 2.6 0.4)	- 0.4	( 0.8	- 2.0)
Adrenocortical insufficiency	Hills et al. (12d)							
	Moore et al. (8c)★	bal. -	75	- 0.6				
Postop. 5 days Burns	Moore et al. (8d)	bal. -		- 18.4				
Renal tubular acidosis	Elkinton et al. (7h)	bal. +	1	7.6		4.8		
	Pines, Mudge (7i)	bal. +	2	6.2	( 5.1 7.2)	2.0	( 5.5	- 1.6)
	Elkinton et al. (7j)	bal. +	3	7.1	( 14.4 3.3)	4.4	( 6.1	3.2)
Uremic acidosis								
Congestive heart failure	Iseri et al. (4a)	bal. +	6	- 12.9	(- 2.8 - 24.8)	3.0	( 5.4	- 0.7)
	Stock et al. (4b)	bal. +	4	- 20.0	(- 8.4 - 33.2)			
	Squires et al. (4c)	bal. +	5	- 22.9	(- 15.6 - 38.4)			
	Hurst et al. (4d)	dil. +	20			- 3.1	( 4.4	- 15.1)
	Warner et al. (8e)**	dil.	14	- 16.1	(- 12.3 - 19.9)			
	Talso et al. (4e)	tis.	8	- 0.8	(- 9.8 2.0)	2.4	( 4.1	- 2.8)

See footnotes to Table 23-IV

Practically therefore, the patient suspected of being dehydrated is given one to three liters of extra water daily until symptoms, principally thirst, are alleviated and urine flow re-established.

**2. Excess** of water may vary much more widely than deficits, ranging up to 40 per cent or more of the normal body water in severely edematous patients (tables 23-II, 23-V) (4a-c). States of overhydration that are patently manifest are less difficult to assess than are minimal states of overhydration. As in respect to deficits excesses may be calculated approximately as follows, where the data are available.

- (a) as equivalent to acute weight gain (if previous weight is known)

Example:

Initial wt. = 70.0 kg.

Final wt. = 72.5 kg.

---

Difference = 2.5 kg.  $\approx$  2.5 liters  $H_2O$  retained

- (b) as equivalent to the measured intake of water minus the sum of the measured losses of water in urine and gastrointestinal fluids and the estimated insensible loss of water.

Example: (during 2 days):

Output: urine = 1600

$H_2O$  vaporization = 2400

---

Total = 4000 ml.

Intake: oral fluids = 4200

i.v. fluids = 1000

$H_2O$  oxidation = 400

---

Total = 5600 ml.

Balance  $H_2O$  = +1.6 liters

- (c) from the fall in serum sodium concentration and the estimated normal total body water,  $W_1$ , (provided there has been no significant loss or gain of electrolytes), as in water-loaded anurics:

$$\text{Excess} = W_2 - W_1$$

$$\frac{Na_{s_1} \times (0.6 \text{ Wt.})}{Na_{s_2}} - (0.6 \text{ Wt.})$$

Example:

Given:  $Wt._1 = 70 \text{ kg.}$

$Na_{s_1} = 140 \text{ mEq./l}$

$Na_{s_2} = 128 \text{ mEq./l}$

Then  $W_1 = 0.6 \times 70 = 42 \text{ liters}$

$W_2 = \frac{140 \times 42}{128} = 46 \text{ liters}$

Excess  $H_2O = 46 - 42 = 4 \text{ liters}$

Practically, the overhydrated anuric patient should have his fluid intake



reasonably restricted and be treated with diuretics and any other measures, e.g., digitalization, bed rest, diuretics, which are needed to produce an effect in the underlying mechanism of his fluid retention, until such time as his signs of peripheral and pulmonary edema disappear. No water restriction is necessary for patients with other forms of edema.

**3. Administration of water** may be a) by the oral route as plain water or as a wide variety of aqueous solutions or natural foods, or b) by parenteral routes as five or ten per cent sugar solutions or electrolyte solutions. Because of the daily need for free water for vaporization and heat expenditure, the intake of water usually should exceed that of electrolyte in respect to their normal ratio in extracellular fluid, i.e., the solution should be "hypotonic." The exceptions to this, of course, are those situations in which specific deficits of electrolytes are being treated. A "hypotonic" water intake can be provided quite simply by ingestion of water, by infusion of five or ten per cent dextrose solution in addition to isotonic electrolyte solution, or by infusion of especially prepared hypotonic electrolyte solution, such as Butler's or Talbot's solutions, described and discussed in the next chapter.

## II. Sodium

The normal daily turnover of sodium ranges between three and nine per cent of the total exchangeable body content (table 23-I) (5a-f); it may be considerably wider in patients on unusual dietary regimes such as very low or very high salt diets.

### A. External Exchanges

Balance is maintained on a very low sodium intake (1 gram sodium chloride  $\approx$  17 mEq., or less) *provided there is no abnormal loss of sodium in urine, gastrointestinal fluid, or sweat*. The normal kidney conserves sodium very well, being able virtually to eliminate this ion from the urine under conditions requiring conservation (5g). The diseased kidney may be unable to conserve sodium and prevent body depletion as in rare cases of chronic glomerulonephritis, nephrosclerosis, pyelonephritis, renal tubular acidosis, or in the polyuric phases of acute renal failure due to tubular damage. Tubular reabsorption and hence renal conservation may be inhibited by a deficiency of adrenocortical steroids or by the administration of mercurial diuretics. Sweat contains sodium in hypotonic concentration but, under conditions of severe heat stress, sweat may be the source of considerable sodium loss (20 to 180 milliequivalents in one to three liters). Abnormal loss of gastrointestinal fluids, because of their similarity in electrolyte composition to extracellular fluid, always results in loss of sodium. When any of these conditions obtain (6a-d), therefore, the sodium

lost must be replaced if depletion is to be prevented and balance maintained. If the output of sodium in urine or gastrointestinal fluid is measured, it can be replaced quantitatively. If not, or in the case of sweat, the sodium loss must be estimated on the basis of probable content in the fluid under consideration.

### *B. Deficits of Sodium*

These may become as high as 50 per cent of the extracellular sodium (approximately 1000 milliequivalents deficit in the average 70-kg. adult or 14 milliequivalents per kg. (tables 23-II, 23-III) (7a-j) before death supervenes from circulatory collapse. Obviously every attempt should be made to repair the deficit long before this point is reached. Deficits more commonly encountered, as in diabetic coma or pyloric obstruction, range from 300 to 600 milliequivalents per average adult (tables 23-II, 23-III). Since sodium loss in clinical situations is almost invariably associated with some degree of water loss, it is impossible to quantitate the former from concentration values alone.<sup>1</sup> If the serum and extracellular concentrations of sodium are low, the replacement of sodium may be thought of in two categories: the sodium that is missing with its proportional share of water, and the sodium that is missing from the water left behind (and so resulting in a lowered concentration). If there is a sodium deficit without a change in extracellular concentration, only the first is pertinent. Deficits of sodium in these two categories can be calculated in terms of milliequivalents in the following ways.

(a) as equivalent to 140 times the loss of water in terms of liters:

- 1) The acute weight loss in kilograms, if known and considered to be due entirely to extracellular fluid loss (a questionable assumption).

Example:

$$\text{Wt. loss} = 1.5 \text{ kg.}$$

$$\text{Na deficit} = 140 \times 1.5 = 210 \text{ mEq.}$$

- 2) The extracellular volume deficit in liters, as estimated, or as measured approximately by dilution of substances such as thiocyanate, inulin, or radiosulfate.

Example:

$$\text{Change in SCN space} = -2.0 \text{ liters}$$

$$\text{Na deficit} = 140 \times 2.0 = 280 \text{ mEq.}$$

<sup>1</sup> One of the authors (J. R. E.) once proposed a formula based on weight, change in concentration of  $\text{CO}_2 + \text{Cl}$  in serum, and change in relative cell volume (hematocrit) (7k). This formula is invalid because: a) change in serum concentration of  $\text{CO}_2 + \text{Cl}$  is frequently different from that in sodium, b) the change in plasma volume is not necessarily linear or proportional to that in total extracellular volume, c) even if it were, relative change in plasma volume cannot be estimated from hematocrit values alone where the tonicity of the plasma in relation to the red cells is changing (hemoglobin measurements are required), and finally d) osmotic shift of water from intracellular fluid requires that the concentration calculation be based on total body water, not extracellular fluid value alone.

- (b) as equivalent to the change in serum sodium concentration times the estimated or measured *total* body water, not the extracellular volume. (The net rise in concentration of total electrolyte in the extracellular fluid must be the same as that in intracellular fluid because of the osmotic shift of freely diffusible water; this holds even if the solute added is in the main restricted to one phase, the extracellular.)

Example:

Given: Normal weight = 70 kg.

Estimated total  $H_2O$  =  $0.58 \times 70 = 40.5$  liters

Observed  $Na_s$  = 125 mEq./l

Then Na deficit =  $15 \times 40.5 = 608$  mEq.

Where there is both an absolute deficit of extracellular fluid (sodium and water in proportional amounts) and a loss of sodium relative to the water left behind in the body, these two methods (a) and (b) should be combined.

Example:

Na deficit with water (a, 1) = 210 mEq.

Na deficit in excess of water (b) = 608 mEq.

---

Total Na deficit = 818 mEq.

Deficits of sodium, calculated as above, should probably not be completely replaced in one 24-hour period. Administration of hypertonic solutions of extracellular electrolyte (sodium) without intracellular electrolyte (potassium) may lead to detrimental shift of water from cells and isotonic solutions may disturb other compensatory adjustments, e.g., cardiac failure because the myocardium has become adjusted to a smaller circulatory load. On the other hand abnormal sodium losses, renal or gastrointestinal, may be continuing during therapy and the calculated sodium requirement is thereby increased.

Practically, therefore, the astute therapist makes the best estimate that he can of the extent of the deficit. The adult with an average degree of sodium depletion of 300 to 600 milliequivalents needs in the vicinity of 200 to 450 milliequivalents, the amount contained in about 1500 to 3000 milliliters of "physiological" 0.85 per cent sodium chloride solution to get him out of the danger zone. Whatever the amount estimated, it is then modified according to the above factors and according to the risk of congestive failure and hypertension on one hand versus circulatory collapse on the other. This is an example of the trial and error nature of intelligent fluid therapy.

### *C. Deficit of Sodium in Excess of Fixed anion*

This disturbance is found in metabolic acidosis and requires separate consideration. Sodium given to combat such a deficit is usually infused as sodium bicarbonate or sodium lactate solution. The effect of such therapy



TABLE 23-IV

OBSERVED AND CALCULATED DEFICITS* OF CERTAIN BODY FLUID CONSTITUENTS IN VARIOUS CLINICAL CONDITIONS												
CONDITION	INVESTIGATORS	TYPE OF STUDY#	NO. OF PTS.	TOTAL		POTASSIUM		INTRACELLULAR		NITROGEN		
				mean	max. milliequivalents	min.	mean	max.	min.	mean	max.	
											grams/kilogram	
Diabetic acidosis	Atchley et al. (3a)	bal. -	2	4.9	( 6.6	3.2)				0.63	( 0.67	0.59
	Butler et al. (7a)	bal. -	1	5.6						0.90		
	Danowski et al. (7b)	bal. +	8	6.0	(11.7	3.2)	5.5	(10.5	2.6)	0.09	( 0.52	-0.34)
	Darrow, Pratt (3b)	bal. +	1	6.1			6.9					
	Nabarro et al. (3c)	bal. +	7	5.0	( 8.3	3.1)	6.0	( 9.0	2.7)	0.60	( 1.07	-0.08)
Gastro-intestinal fluid loss and starvation	Darrow (7c)††	bal. +	6	11.3	(17.3	6.0)				0.84	( 1.24	0.19)
	Tarail, Elkinton (7d)	bal. +	4	10.7	(17.7	5.5)	9.7	(15.6	5.5)	0.12	( 0.76	0.33)
	Darrow et al. (7e)††	bal. +	8				10.4	(15.1	3.0)			
	Danowski et al. (7f)‡	bal. +	4	15.6	(21.7	13.3)	8.4	(12.7	6.0)	1.59	( 2.74	0.44)
	Elkinton et al. (7g)	bal. +	4	10.7	(17.7	5.5)	9.7	(15.6	5.5)	0.14	( 0.58	0.31)
	Schwartz, Relman (8a)	bal. +	2	11.4	(12.0	10.8)	11.2	(11.3	11.0)			
	Eliel et al. (8b)†	dil. -	1									
	Mudge, Vislocki (3d)	tis. -	3	3.3	( 7.8	0 )	3.0	( 7.5	0 )			
Adrenocortical insufficiency	Harrop et al. (12c)§											
	Elkinton (3e)	bal. +		-0.4	(-0.2	-0.6)	-0.4	(-0.1	-0.7)	0.02	( 0.08	-0.06)
Postop. 5 days	Hills et al. (12d)											
	Moore et al. (8c)*	bal. -	75	3.0						0.69		
	Moore et al. (8d)	bal. -		5.1						-0.74		
Renal tubular acidosis	Elkinton et al. (7h)	bal. +	1	14.7			16.5			-0.93		
	Pines, Mudge (7i)	bal. +	2	3.0	( 4.5	1.5)	2.3	( 3.9	0.6)			
Uremic acidosis	Elkinton et al. (7j)	bal. +	3	5.3	( 8.6	2.0)	4.9	( 8.6	2.5)	0.15	( 0.65	-0.12)
	Iseri et al. (4a)	bal. +	6	5.7	(10.6	1.5)	5.4	( 9.2	0.9)	0.18	( 0.57	-0.37)
Congestive heart failure	Stock et al. (4b)	bal. +	4	-2.7	(-0.6	-3.6)	-0.3	( 1.0	-1.8)	-0.97	(-0.62	-1.61)
	Squires et al. (4c)	bal. +	5	7.2	(15.4	-2.1)	6.8	(13.0	-0.7)	0.50	( 1.15	-0.21)
	Hurst et al. (4d)	dil. +	20									
	Warner et al. (8e)**	dil.	14									
	Talso et al. (4e)	tis.	8	5.5	(11.1	-1.0)	5.5	(11.3	1.4)			

- \* Deficits are presented as positive values, therefore those with a minus sign represent negative deficits or excesses.
- # Types of study are indicated as follows:
  - bal. metabolic balance study; a minus sign indicates that the deficit was measured during its development, a positive sign indicates that the deficit was quantitated as equivalent to uptake during restoration. This latter is based upon the not-necessarily-always-valid assumption that over-shoot does not occur; but only those studies were taken in which the patient had an opportunity to come to equilibrium (as regards amount and duration of intake).
  - dil. measurement by isotope dilution or volume of distribution of an exogenous solute.
  - tis. measurement by tissue analysis (skeletal muscle) and calculation for the total body by assuming: 1) that this tissue is 40 per cent of the total body weight, and 2) that the only abnormality is in the muscle (an artificial assumption).
- ⊕ Calculated as change in the chloride space.
- ⊗ Calculated in relation to change in the chloride space.
- Calculated in excess of nitrogen balance; K:N ratios which were used ranged from 2.4 to 3.0 mEq. per gram.
- !! Cases of acute epidemic diarrhea in infants, therefore not included in next table calculated for the average adult.
- ∞ Cases of pyloric stenosis and vomiting in infants, also not included in next table. This series includes one case, W.H., from Elkinton et al. (8p).
- ♦ Dilution of bromide and Na<sup>24</sup>.
- ★ Composite picture of 75 cases, see Figure
- \*\* Dilution of Na<sup>24</sup>.
- § Patient of Elkinton was an Addisonian treated for initial acute crisis; that of Harrop et al. was an Addisonian allowed to relapse for 4 days; those of Hills et al. were hypertensives with adrenocortical ablation who were allowed to relapse for 2 days.

TABLE 23-V

OBSERVED AND CALCULATED DEFICITS\* OF CERTAIN BODY FLUID CONSTITUENTS IN VARIOUS CLINICAL CONDITIONS  
Expressed in units per average adult of 70 kilograms body weight and 1.73 M<sup>2</sup> surface area

CONDITION	INVESTIGATORS	TYPE OF STUDY#	NO. OF PTS.	TOTAL			WATER			EXTRACELLULAR <sup>Ⓐ</sup>			CHLORIDE		
				mean	max.	min.	liters	mean	max.	min.	mean	max.	min.	max.	min.
Diabetic acidosis	Atchley <u>et al.</u> (3a)	bal.-	2	6.2	( 6.4	5.9)		0.8			172	( 210	133)		
	Butler <u>et al.</u> (7a)	bal.-	1					5.3	(14.5	1.1)	280	(1830	77)		
	Danowski <u>et al.</u> (7b)	bal.+	8					5.6			665				
	Darrow, Pratt (3b)	bal.+	1	8.0				2.9	( 6.1	1.4)	832				
	Nabarro <u>et al.</u> (3c)	bal.+	7	4.6	( 6.4	3.1)					360	( 705	216)		
Gastro-intestinal fluid loss and starvation	Tarail, Elkinton (7d)	bal.+	4					1.0	( 4.9	- 3.8)	308	( 650	- 105)		
	Elkinton <u>et al.</u> (7g)	bal.+	4					3.4	( 6.5	0.2)	730	( 953	250)		
	Schwartz, Relman (8a)	bal.+	2												
	Eliel <u>et al.</u> (8b) <sup>†</sup>	dil.-	1					1.8							
	Mudge, Vislocki (3d)	tis.-	3	0.1	( 0.3	0 )		1.2	( 2.0	0.1)	252	( 400	112)		
Adrenocortical insufficiency	Harrop <u>et al.</u> (12c) <sup>§</sup>							0.2			144				
	Elkinton (3e)	bal.+	1	1.6				8.6			1150				
	Hills <u>et al.</u> (12d)			0.3	( 1.2	- 0.5)		0.8	( 1.8	- 0.2)	115	( 283	40)		
Postop. 5 days	Moore <u>et al.</u> (8c) <sup>★</sup>	bal.-	75												
	Moore <u>et al.</u> (8d)	bal.-													
Renal tubular acidosis	Elkinton <u>et al.</u> (7h)	bal.+	1					0.7			-112				
	Pines, Mudge (7i)	bal.+	2					1.4	( 2.7	0.1)	0	(-140	- 140)		
	Elkinton <u>et al.</u> (7j)	bal.+	3					0.2	( 3.4	- 2.1)	7	( 231	- 154)		
Uremic acidosis															
Congestive heart failure	Iseri <u>et al.</u> (4a)	bal.+	6	- 8.6	(-1.5	-14.4)		-7.1	(-1.9	-13.0)	-644	(- 7	-1310)		
	Stock <u>et al.</u> (4b)	bal.+	4	-10.0	(-4.6	-18.1)					-1265	(-602	-2080)		
	Squires <u>et al.</u> (4c)	bal.+	5	-15.2	(-9.0	-26.8)		-7.6	(-5.0	-12.0)	-994	(-595	-1530)		
	Hurst <u>et al.</u> (4d)	dil.+	20	- 8.6	(-0.7	-20.5)									
	Warner <u>et al.</u> (8e) <sup>**</sup>	dil.	14												
	Talso <u>et al.</u> (4e)	tis.	8	- 8.6	(-7.0	-10.8)		-5.2	(-4.3	- 5.5)	- 91	(-175	- 398)		

See footnotes to Table 23-IV



on the serum sodium concentration may be calculated from an assumed or estimated total body water, as immediately above in (b). The effect on the serum bicarbonate and total carbon dioxide concentration, usually the therapeutic goal, is somewhat less predictable. The reason for this is that, in a given individual patient, the fraction of the sodium so given, which enters the "non-chloride" or intracellular space, is quite unpredictable. One of us (J. R. E.) has shown in patients with uremic acidosis that this fraction may vary anywhere from 30 to 100 per cent of the sodium administered (7j). Hartmann's formula for the dose of sodium lactate was:

Give: 1 ml. molar lactate per 1 kg. wt. to raise serum  $\text{CO}_2$  content 1 vol. per cent

which, translated into current units is:

Give: 1 mEq. Na lactate per 1 kg. wt. to raise serum  $\text{CO}_2$  content approximately 0.5 mM per liter

This formula was derived empirically from the observed effects of sodium lactate therapy and simply represents the average effect found. It means that the average distribution of sodium given as lactate was approximately 50 per cent of the body weight or that one-half or more of the sodium left the "extracellular" space.

The practicality, therefore, is to calculate that about one-half of the sodium given and retained will exert an effect in the serum bicarbonate and total carbon dioxide concentration according to the estimated extracellular volume.

Example: Given: Estimated extracellular volume = 0.2 Wt. = 14 liters  
 Initial serum  $\text{CO}_2$  = 10 mM./l.  
 Dose of Na lactate, 4 ampules M Sol., 40 ml. each = 160 mEq.

Then: (a) Rise in serum  $\text{CO}_2$  =  $\frac{\frac{1}{2} \times 160}{14} = 6 \text{ mM/l}$

Final serum  $\text{CO}_2$  conc. =  $10 + 6 = 16 \text{ mM/l}$

(b) If  $\frac{3}{4}$  of the Na enters cells, rise in serum  $\text{CO}_2$  conc. =  $\frac{\frac{1}{4} \times 160}{14} = 3 \text{ mM/l}$

#### D. Sodium Excess

Excess of extracellular sodium is almost always associated with an excess of water and is clinically demonstrable as edema. As in the case of water, excesses of the ion vary more widely than do deficits (4a-e, 5c) and have been measured in amounts up to 50 per cent or more of the normal extracellular content (tables 23-III, 23-VI). It is seldom necessary to estimate

TABLE 23-VI  
OBSERVED AND CALCULATED DEFICITS\* OF CERTAIN BODY FLUID CONSTITUENTS IN VARIOUS CLINICAL CONDITIONS

CONDITION	INVESTIGATORS	TYPE OF STUDY#	NO. OF PTS.	mean	TOTAL max.	SODIUM		INTRACELLULAR*	
						min. milliequivalents	mean	max.	min.
Diabetic acidosis	Atchley <u>et al.</u> (3a)	bal.-	2	409	( 468	350)			
	Butler <u>et al.</u> (7a)	bal.-	1	331	( 1760	343)	- 119	( 154	- 525)
	Danowski <u>et al.</u> (7b)	bal.+	8	728					
	Darrow, Pratt (3b)	bal.+	1	933	( 667	384)			
	Nabarro <u>et al.</u> (3c)	bal.+	7	500					
Gastro-intestinal fluid loss and starvation	Tarail, Elkinton (7d)	bal.+	4	510	( 1050	133)	- 216	( 168	- 476)
	Elkinton <u>et al.</u> (7g)	bal.+	4	0	( 790	- 812)	- 652	( 0	- 997)
	Schwartz, Relman (8a)	bal.+	2				- 755	(-755	- 755)
	Eliel <u>et al.</u> (8b)	dil.-	1	-1580			-1240		
	Mudge, Vislocki (3d)	tis.-	3	- 328	(- 42	- 854)	- 504	(- 77	-1120)
Adrenocortical insufficiency	Harrop <u>et al.</u> (12c)§			177					
	Elkinton (3e) Hills <u>et al.</u> (12d)	bal.+	1	124	( 190	27)	- 24	( 53	- 140)
Postop. 5 days Burns	Moore <u>et al.</u> (8c)*			- 42					
	Moore <u>et al.</u> (8d)	bal.-	75	-1290					
Renal tubular acidosis	Elkinton <u>et al.</u> (7h)	bal.+	1	532	( 505	358)	336	( 385	- 112)
	Pines, Mudge (7i)	bal.+	2	435	( 1010	231)	140	( 427	- 224)
	Elkinton <u>et al.</u> (7j)	bal.+	3	497			308		
Uremic acidosis	Iseri <u>et al.</u> (4a)	bal.+	6	- 903	(- 196	-1735)	210	( 378	- 49)
	Stock <u>et al.</u> (4b)	bal.+	4	-1400	(- 588	-2325)		( 308	-1055)
	Squires <u>et al.</u> (4c)	bal.+	5	-1600	(-1090	-2690)	- 217		
	Hurst <u>et al.</u> (4d)	dil.+	20						
	Warner <u>et al.</u> (8e)**	dil.	14	-1125	(- 860	-1390)			
Congestive heart failure	Talso <u>et al.</u> (4e)	tis.	8	- 56	( 140	- 686)	168	( 287	- 196)

See footnotes to Table 23-IV

this excess quantitatively prior to treatment and diuresis. Excess of intracellular sodium is frequently found in potassium depletion and may amount to as much as ten milliequivalents per kilogram weight. While it is impossible to quantitate this cellular increment of sodium, prior to potassium therapy, it means that once the latter is started less sodium than chloride is required from exogenous sources to replete and to maintain the extracellular fluid.

### III. Chloride

The daily turnover and total body content of this ion are very close in magnitude to those of sodium (table 23-I) (8c,f). This is due to the fact that next to sodium it is the largest ionic constituent of extracellular fluid, and to an even greater extent than sodium, is excluded from most tissue cells.

#### A. Balances, Deficits and Excesses of Chloride

The conditions of excretion in urine, gastrointestinal fluid, and sweat, which underlie the *maintenance of balance* are essentially the same as for sodium. The magnitudes of deficits are roughly the same as those for sodium, the principal differences being due to the normal ratio in extracellular fluid of sodium to chloride of 1.3 to 1, and the differential transfers of sodium in respect to chloride into and out of cells. These latter are primarily found in states of potassium deficiency associated with metabolic alkalosis. For these two reasons the requirement of chloride is generally less than that for sodium, and straight sodium chloride solutions with equi-molar amounts of the two ions are therefore less than "physiological." Quantitative replacement is seldom calculated for the chloride ion *per se*. Where the deficit of chloride is proportionally less than that of sodium, replacement of the sodium in excess of chloride and fixed anion is calculated as outlined in the preceding section. Where the deficit of chloride is proportionally greater than that of sodium, the ion can be given as ammonium chloride or potassium chloride. The latter salt is usually preferable since serious conditions of relative, and absolute, extracellular deficit (metabolic alkalosis) are commonly associated with potassium deficiency. Under these circumstances the quantitative assessments are primarily those of the cations, sodium and potassium, with the final adjustment of the chloride content depending on the linked transfers in tissues and kidneys.

### IV. Potassium

The daily turnover of potassium ranges between 50 and 150 milliequivalents in the average adult and is equivalent to 1.5 to five per cent of the total body content (table 23-I) (9a-c).



TABLE 23-VII

OBSERVED AND CALCULATED DEFICITS\* OF CERTAIN BODY FLUID CONSTITUENTS IN VARIOUS CLINICAL CONDITIONS

CONDITION	INVESTIGATORS	TYPE OF STUDY#	NO. OF PTS.	POTASSIUM			INTRACELLULAR			NITROGEN	
				mean	TOTAL max.	min. milliequivalents	mean	max.	min.	mean	TOTAL max. grams
Diabetic acidosis	Atchley et al. (3a)	bal.-	2	343	( 462	224)				44.1	( 46.8
	Butler et al. (7a)	bal.-	1	400			214			62.0	41.3)
	Danowski et al. (7b)	bal.+	8	420	( 820	224)	385	( 735	182)	6.1	( 36.4
	Darrow, Pratt (3b)	bal.+	1	428			484				- 23.9)
	Nabarro et al. (3c)	bal.+	7	347			422			38.8	( 75.0
Gastro-intestinal fluid loss and starvation	Tarail, Elkinton (7d)	bal.+	4	385	( 637	259)	350	( 490	266)	8.4	( 53.2
	Elkinton et al. (7g)	bal.+	4	750	(1240	385)	680	(1090	385)	9.8	( 40.6
	Schwartz, Relman (8a)	bal.+	2	800	( 840	755)	783	( 792	770)		- 21.7)
	Eliel et al. (8b)	dil.-	1								
	Mudge, Vislocki (3d)	tis.-	3	231	( 547	0)	210	( 525	- 21)		
Adrenocortical insufficiency	Harrop et al. (12c)§										
	Elkinton (3e)	bal.+	1	- 25	(- 16	- 42)	- 30	(- 10	- 50)	1.6	( 8.3
Postop. 5 days Burns	Hills et al. (12d)										- 3.9)
	Moore et al. (8c)*	bal.-	75	210						48.4	
Renal tubular acidosis	Moore et al. (8d)			357						-51.8	
	Elkinton et al. (7h)	bal.+	1	1027			1153			-65.0	
	Pines, Mudge (7i)	bal.+	2	210	( 315	105)	161	( 247	42)		
	Elkinton et al. (7j)	bal.+	3	471	( 603	140)	343	( 603	175)	10.5	( 45.5
											- 8.5)
Uremic acidosis											
	Iseri et al. (4a)	bal.+	6	400	( 742	105)	378	( 644	63)	12.6	( 40.0
	Stock et al. (4b)	bal.+	4	-182	(- 42	-252)	- 21	( 70	-126)	-68.0	(-43.4
	Squires et al. (4c)	bal.+	5	504	(1080	-147)	476	( 910	- 49)	35.0	( 80.0
	Hurst et al. (4d)	dil.+	20								- 14.7)
Congestive heart failure	Warner et al. (8e)**	dil.	14								
	Talso et al. (4e)	tis.	8	385	( 778	- 70)	385	( 790	98)		

See footnotes to Table 23-IV

### A. Balance

Balance is maintained on even lower intakes provided that renal and adrenocortical function are normal, that there is no abnormal gastrointestinal loss, and that the patient is not in a catabolic phase. In normal subjects *not under stress* renal conservation is as good as that for sodium, and on diets which maintain nitrogen balance but which contain only 15 milliequivalents of potassium, the renal excretion reaches this level in three to five days (10a, b). In patients who have normal kidneys but who are undergoing the stress of other types of disease or of the postoperative period, the renal excretion may vary widely up to 85 milliequivalents per day when the intake is zero (7d) (tables 23-IV, 23-VII). These patients obviously require the ion to keep them in balance. Renal excretion of potassium is accelerated by the administration of desoxycorticosterone, ACTH, and cortisone as discussed in chapter 17, and by sodium loading (10c). In general, patients who are taking food by mouth are getting enough potassium since it is a principal constituent of vegetable as well as of animal cells. The daily excretion of potassium in the stool of normal subjects ranges between 6 and 26 milliequivalents (10d).

### B. Potassium Losses

Deficits of potassium cannot be quantitated readily prior to therapy because of the predominately intracellular position of the ion (10e). Deficits can be estimated by analysis of tissue biopsies, especially skeletal muscle, and by isotope dilution, but these are usually experimental technics. During therapy the deficit can be assessed in terms of potassium retained, but this requires the accurate measurement of intake and output until the patient comes into equilibrium and is at best a bit of hindsight as far as therapy goes. In addition the ability of normal cells to store additional supplies of potassium for temporary periods of time can give a false impression of deficit replacement. The therapist, therefore, must rely on the experience of himself and others as to the probable degree of deficit likely to be involved in the clinical disturbance at hand, and finally to judge according to the response of the patient to therapy. The range of potassium deficiency varies widely and may amount to as much as 800 to 1000 milliequivalents in the average adult (tables 23-IV, 23-VII). Deficits of 200 to 400 milliequivalents are much more common.

*Practically*, one administers one or two liters per day of one of the potassium-containing solutions listed in the next chapter until the serum potassium concentration returns to the normal range. These solutions supply 60 to 80 milliequivalents per liter of solution. Two liters per day for two days supplies 240 to 320 milliequivalents. A small allowance must be made for

concurrent excretion. More dilute solutions, also listed in the tables in chapter 24, have been recommended by pediatricians such as Darrow, Butler and Talbot, but their use in repair of deficits of the magnitude mentioned above requires a rather large volume of water. Concentrations of potassium of 20 to 35 milliequivalents per liter are said to be safer but we have never seen dangerous extracellular levels produced by the judicious use of the stronger potassium solutions mentioned above. Finally, 500 milliliters to one liter per day of these 60 to 80 milliequivalents per liter potassium solutions will prevent the development of serious deficiencies of the ion by patients on low potassium intake (parenteral fluids), and the multiple electrolyte solutions (Darrow's, Butler's, Talbot's: described in chapter 24) are ideal for this purpose.

### *C. Potassium Surplus*

Excesses of potassium in intracellular fluid are no more easily quantitated than deficits and are perhaps of less clinical significance. Excess of extracellular potassium is particularly important in relation to water, i.e., the concentration, because of potential cardiotoxicity (chapter 9), and this level is readily measured in serum. The amount of potassium to be removed by resins or dialysis in such a case, however, is not simply calculated as the product of this concentration and the extracellular fluid volume since the extracellular portion of the ion is in constant equilibrium with the intracellular fraction. Some intracellular potassium must be removed as well. Therapy, however, is guided by the extracellular concentration and the electrocardiogram.

## **V. Magnesium**

The daily turnover of this ion ranges between 20 to 50 milliequivalents or 1.3 to 3.6 per cent of the total body content (table 23-I) (1b, 11a-e). Balance is easily maintained, as in the case of potassium, when the patient is eating normal cellular foods. Very little is known as to the range or efficiency of renal conservation on a low-magnesium or a magnesium-free diet. Deficits have been described in diabetic acidosis and in patients on parenteral fluids containing no magnesium (11d, e). The magnitude, as measured by balance studies, may range between 50 to 70 milliequivalents in the average adult. Treatment, as in the case of potassium, must be empiric and must be guided by a rise in the serum concentration of the ion. Excesses have also been described under the same condition of inadequate renal function which lead to retention of potassium. The indications for therapy of hypermagnesemia, however, are not clearly understood. It may even be beneficial because of antagonistic action of magnesium to potassium on the heart (11f).



## VI. Bicarbonate and Carbon Dioxide

These constituents will not be treated separately here since the extracellular fluid content is determined primarily by the difference between the fixed cation and fixed anion content. The abundant availability of carbon dioxide from metabolic sources can be emphasized by recognition of the fact that the daily basal turnover of this substance is approximately 1500 to 1800 per cent of the total body content (table 23-I). This is of an entirely different order of magnitude from those of the other "structural" constituents of the body fluids.

## VII. Foodstuffs

### *A. Carbohydrate*

Sugars are usually given to the limit of tolerance in a sick patient for the purpose of providing as many calories as possible to prevent ketosis and to mitigate protein catabolism. The minimum requirement for this purpose is about 140 grams of dextrose in the average adult (70 kg., 1.73 square meter surface area) or 2 grams per kg. weight or 80 grams per square meter. Such a dose is contained in three liters of five per cent or 1.5 liters of 10 per cent dextrose solutions. The maximum limit is about 500 grams per adult, set by glycosuria, and overhydration, and the practical difficulties attendant upon nausea or distension and venous thrombosis. Since the daily basal caloric expenditure is between 1800 and 2000 calories for the average adult, even optimum carbohydrate administration cannot completely meet energy requirements and completely prevent tissue catabolism. These limitations emphasize the wisdom of employing gastrointestinal alimentation whenever possible and the need for development of methods for administering fat intravenously.

### *B. Protein and Protein Precursors*

The minimum daily requirement of nitrogen to maintain balance has been thought to be about 6 grams per adult though equilibrium can be reached in lesser amounts. Much larger amounts are required in sick and febrile patients. When protein cannot be given through the gastrointestinal tract, casein hydrolysates can be used intravenously. One liter of the solutions commercially available provides about six grams of nitrogen.

## VIII. Colloidal or Blood and Plasma Expanders

The requirement of these constituents depends more on the dynamic state of the circulation than on a quantitative estimate of deficits. Formulae have been devised for the calculation of the quantity of plasma required to replace that lost from the vascular system in burns, but usually the

quantity given is empiric. Whole blood replacement in hemorrhagic shock is likewise guided by both the state of the circulation and by some estimate of the amount of blood lost. This may be a matter of quite a few liters in the massive hemorrhage sometimes encountered in trauma, gastrointestinal bleeding, and cardiac surgery. Plasma, blood, and plasma expanders are most commonly given in multiples of the 250 and 500 ml. units. Concentrated albumin as prepared by the Red Cross and the military services is a 25 per cent solution in a 100-ml. unit (25 grams of albumin). Two such units or 200 ml. given intravenously is a common dose in the treatment of traumatic shock.

## **IX. Common Dilemmas in the Treatment of Fluid Disturbances**

### *A. Sodium for Renal and Circulatory Failure in Patients with Edema and Cardiovascular Disease*

Not infrequently a patient in the postoperative period following gastrointestinal surgery is found to have progressive oliguria, a rising BUN or NPN, and possibly a tendency to hypotension. Hyponatremia may be present. The possibility is real that the patient is suffering from impaired circulation, including the renal circulation, due to a sodium deficit. On the other hand the patient may have cardiovascular disease with actual or potential heart failure (some edema and hypertension), and there may be edema of his surgical wound. Under these circumstances the surgeon and the cardiologist are understandably reluctant to administer much sodium. This is particularly true in the present age of low sodium intakes for both postoperative hyperadrenocorticism and cardiovascular disease (congestive failure and hypertension). The particular solution of the dilemma is most likely to depend upon the prejudices of the responsible therapist. The hazards of shock and progressive renal failure must be weighed against those of pulmonary and peripheral edema and hypertension. In the opinion of the authors a careful therapeutic trial of an increased intake of sodium is indicated in this situation. Improved circulation and renal function is worth little extra peripheral edema or a few more pulmonary rales.

This dilemma is of course paramount in patients with congestive heart failure and hyponatremia (the "low-salt syndrome"), and not infrequently occurs in hypertensive patients without edema. In both of these situations the patient has been on a very low sodium intake and probably has had mercurial diuretics frequently given as well. If the patient does not respond favorably to sodium, then he has hyponatremia of some origin other than sodium depletion.

### *B. Sodium for Metabolic Acidosis in Patients with Edema and Hypertension*

This dilemma is very similar to the one delineated above. It usually occurs in the uremic patient with acute or chronic renal insufficiency. While

it is desirable to mitigate the metabolic acidosis, it is undesirable to increase edema, to exacerbate hypertension, or to induce convulsions. Therapy therefore is guided accordingly: more sodium bicarbonate or lactate is given in the absence of these complications; less in their presence. It has even been advocated that alkaline sodium salts should not be given at all in uremic acidosis. To the authors this view seems unnecessarily conservative.

### *C. Potassium for Hypokalemia in Patients with Renal Insufficiency*

This dilemma occasionally arises and can only be resolved by careful consideration of the individual case. Patients with chronic renal insufficiency and oliguria usually have elevated levels of serum potassium, and this occasionally occurs in those who are polyuric. Potassium wasting in the urine is a rare consequence of renal disease: it occurs in the polyuric phase of acute tubular damage and in certain peculiar and bizarre cases of chronic renal disease. These points are discussed in greater detail in chapter 12. In these circumstances potassium should be given in amounts according to the urinary losses and the level of serum potassium. In the more common cases of chronic renal insufficiency, e.g., chronic glomerulonephritis, nephrosis, nephrosclerosis, chronic pyelonephritis, and polycystic disease, hypokalemia may supervene as the result of loss of gastrointestinal fluid. In such a situation potassium may be given but this should be done very cautiously as the tolerance of such patients for the ion is low and potassium intoxication with hyperkalemia easily induced. However, recent evidence suggests that potassium deficiency *per se* may lead to tubular damage and renal dysfunction. It is probable, therefore, that with increased knowledge and experience the indications for potassium in renal failure will be broadened.

### *D. Chloride for Hypochloremia in Vomiting Uremics*

This not uncommon dilemma arises when patients with renal insufficiency leading to retention of phosphates, sulfates, and organic acids, lose large amounts of acid gastric fluid (HCl). The resultant depletion of chloride and hypochloremia may cause a metabolic alkalosis which cancels or outbalances the metabolic acidosis of the uremia. Since the latter may be progressive, and subsequently may be made worse by administered chloride ion, it sometimes is difficult to determine how much chloride to give and in what form. The severity of the net disturbance in pH must be a major factor in the decision; severe alkalosis with tetany warrants treatment with chloride whatever the future course anticipated. This dilemma is illustrated in fig. 23-2, which shows a case of severe alkalosis with tetany superimposed on acute renal and hepatic failure. These two latter conditions contraindicated the use of potassium or ammonium salts; hydrochloric acid was therefore given. This is an extreme example; more com-



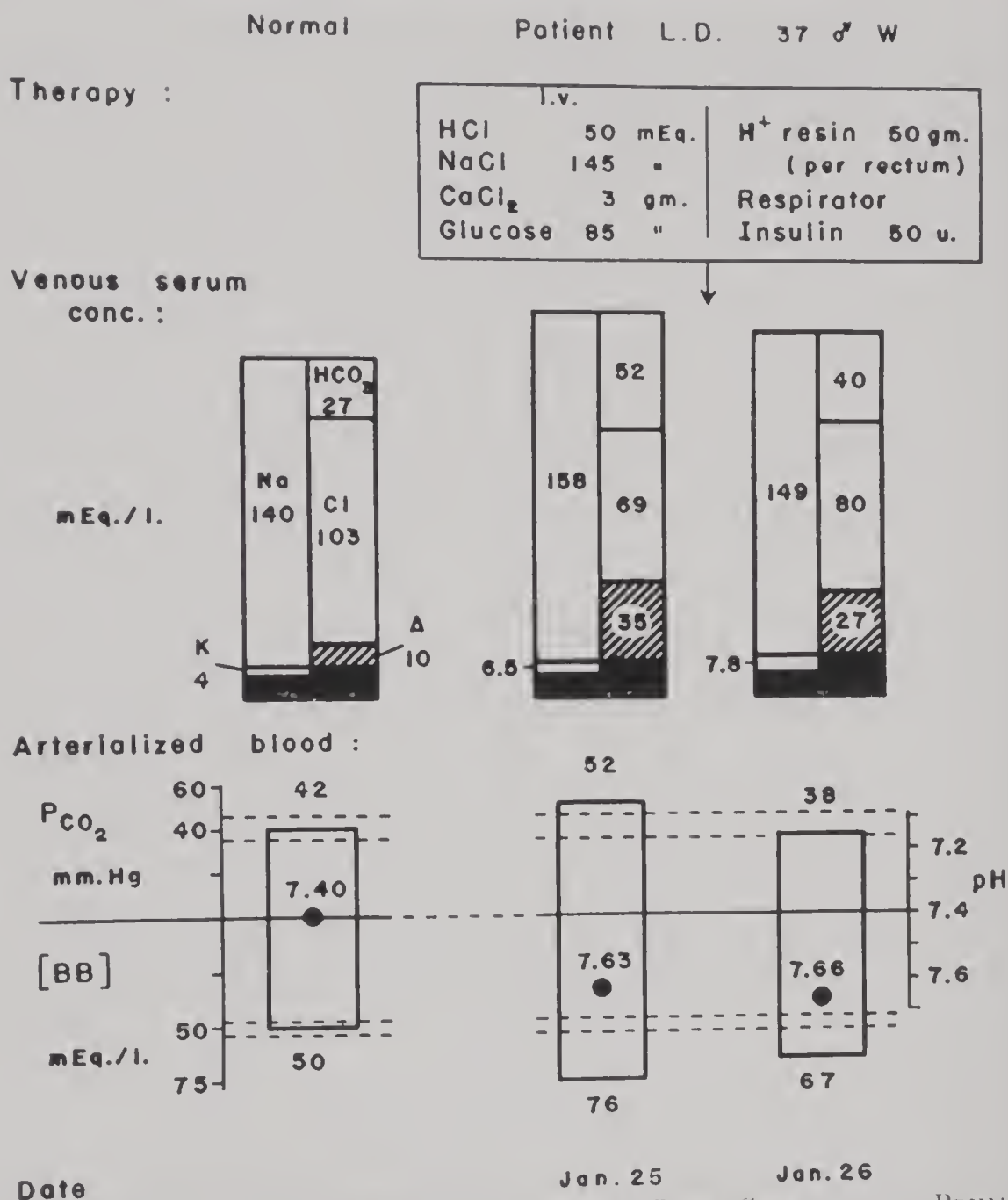


FIG. 23-2. A COMPLEX PROBLEM IN FLUID THERAPY: THREE SIMULTANEOUS PRIMARY ANION-CATION DISTURBANCES IN A CASE WITH GASTRO-INTESTINAL OBSTRUCTION SUPERIMPOSED ON ACUTE RENAL FAILURE

Electrolyte and anion-cation patterns are plotted as in figs. 11-5 and 11-4.

Data are given for the 14th day of anuria resulting from a severe hemolytic transfusion reaction; the patient had been dialyzed twice on a Skeggs-Leonards artificial kidney. Course was complicated by acute pancreatitis (exploratory laparotomy), hepatitis, and extensive gastro-intestinal hemorrhage; postoperative distension required constant gastric suction.

During the 48 hours subsequent to the second dialysis and prior to the chemical findings of Jan. 25th as shown, 4650 ml. gastric fluid were withdrawn; this resulted in a severe hypochloremic metabolic alkalosis despite the prior metabolic acidosis due to the renal retention of phosphates, sulfates, and organic acids (measured as  $\Delta = Na - (CO_2 + Cl)$ ). The patient developed severe tetany and became comatose. The major therapeutic requirement was chloride ion in excess of sodium ion; KCl

monly a mild degree of vomiting by the uremic merely ameliorates the course of his metabolic acidosis.

**SUMMARY:** A knowledge of the net daily changes in body water and in the chief electrolytes under conditions of water deprivation, starvation, vomiting, diarrhea and sweating and of the limitations imposed by circulatory or renal disturbances provides the information necessary for estimation of replacement and maintenance needs. This involves calculation of the daily intake of water and solutes and measurement, estimation, and analysis of the output via urine, bowel, skin, lungs as well as in drainage.

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was contraindicated because of the already dangerous levels of potassium,  $\text{NH}_4\text{Cl}$  was contraindicated because of the danger of  $\text{NH}_3$  toxicity in the presence of hepatic damage. Accordingly  $\text{HCl}$  was infused, first as a 0.01N and then as 0.05N (or 50 mEq./l.) solution in 5% glucose, with a resultant rise in extracellular chloride level (on Jan. 26th).  $\text{H}^+$  resin was given by enema for potassium removal as well as for an acidifying effect.

The patient's tetany improved but cyanosis and atelectasis led to the use of mechanical chest respirator. This in turn resulted in a third primary disturbance: a respiratory alkalosis due to the lowering of the alveolar and arterial  $\text{Pco}_2$ . The patient died on the 26th. (From Bluemle and Elkinton (12c)).

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## *Chapter 24*

# **TECHNICS AND SOLUTIONS IN REPLACEMENT THERAPY**

The diagnosis of disturbances in the body fluids and the assessment of fluid requirements have been discussed in the preceding two chapters. In this chapter are presented the various therapeutic procedures by which the physician acts on such judgment to restore the patient's body fluids to a healthier state of dynamic equilibrium.

### **I. General Principles**

#### *A. The Patient as a Whole*

The practice of medicine in this field as in others is an art as well as a science. Consideration of the patient as a person is imperative to successful therapy. He should be comforted, reassured, and within the limits of possibility and wisdom, given an understanding of his situation. The proper goal of the physician is not alone the solution of an intriguing physiologic problem, but the return of the patient to the best possible state of health and function as a member of society.

Due consideration must be given to aspects of the patient's disease state other than the disturbances in body fluid structure and function. Infection, trauma, metabolic derangement or malignancy may primarily determine the outcome of the illness and limit even the scope of the fluid therapy that should be undertaken. Thus the wise physician views the patient's body fluid abnormalities in their proper relation to the total disease and within this broader framework exercises his skill and judgment in managing the specific disturbances involved.

Due consideration must also be given to the various dimensions of body fluid abnormality. As indicated in Parts I and II these may involve disturbances in volume, in concentration, in relative ion proportions, and in regional distribution. Even in disease states regulatory organs of the body fluids make homeostatic adjustments. Concentration may be sacrificed to

volume, relative ion concentration to total ion concentration, volume and flow in one region to volume and flow in another, etc. The therapist, therefore, when he alters one of these dimensions, must take cognizance of the effect of the therapy on other dimensions and usually he must effect a compromise.

Furthermore, the physician seldom knows the absolute degree of change from normal of most of the dimensions of the body fluids. Hence it behooves him to proceed with caution, to attempt to induce alterations in the right direction, to remember that concurrently with his therapeutic measures the pathological processes which produced the disturbances may be continuing, and to recognize that the cooperating organs of regulation of the body fluids have their homeostatic limitations.

### *B. Types of Therapeutic Procedures*

The procedures available to the physician for treating body fluid disturbances are many. They include the administration by enteral or parenteral routes of solutions or materials containing various components of body fluids, the influencing of fluid distribution by position, drugs, enzymes such as hyaluronidase, etc., the alteration of output of various fluid constituents from the body through the normal organs of excretion (the kidneys, gastrointestinal tract, lungs and skin), the use of exchange resins in the intestinal tract, and dialysis by peritoneal or gastrointestinal lavage or by extracorporeal hemodialysis in some type of "artificial kidney."

For the judicious use of these techniques, in various combinations, it must be remembered that a dynamic and not a static structure is being influenced. Deficits or excesses of particular constituents represent new dynamic equilibria or steady states. Keeping in mind the limitations of our current knowledge, these procedures are intended to move these dynamic equilibria in a direction which makes for greater health of the organism as a whole.

## **II. Fluid Administration Via the Gastrointestinal Route**

As far as circumstances permit, fluids should be given by the gastrointestinal tract rather than by parenteral routes. This is the normal port of entry of nutritional and fluid constituents. Its use permits a much wider choice of such constituents with much less hazard in respect to immunological reactions or to overloading the circulation. Contraindications to the administration of fluids by this route usually consist of profound weakness, unconsciousness, nausea, vomiting, gastric hemorrhage, gastrointestinal obstruction, ileus, or gastrointestinal or abdominal surgery.

### *A. Oral*

Some of the natural fluids and prepared solutions to be drunk or to be given through a tube into the stomach are shown in table 24-I.

TABLE 24-I.

FLUIDS SUITABLE FOR ORAL AND GASTROINTESTINAL FEEDINGS, AND CONCENTRATED POWDERED FOOD PRODUCTS FOR THEIR PREPARATION										
PREPARATION	VOL- UME	Cl	Na	K	N	PROTEIN EQUIV.	CARBO- HYDRATE	FAT	CALORIES	COMMERCIAL
	(ml.)	(mEq.)	(mEq.)	(mEq.)	(gm.)	(gm.)	(gm.)	(gm.)		
A. ORAL AND GASTRIC:										
1. Sugar solution	1000						100		410	
2. Emergency salt solution *	1000	90	121							
3. Ginger ale	1000	3	3	0	0	0	90	0	360	
4. Orange juice	1000	0	3	41	0.9	8	110	0	490	
5. Whole milk	1000	30	22	41	5.0	31	49	39	696	
6. Dialyzed milk (Lonalac) +	1000	26	1	52	5.3	33	49	31	625	Mead Johnson
7. Tea, weak (1 cup)	150	0	0	1	0	0	5	0	20	
8. Coffee, weak (1 cup) *	150	0	0	4	0.7	4	5	0	36	
9. High fat-low K <sub>s</sub> (Lipomul) ‡	1000	0	7	0	0	0	100	400	4000	Upjohn
10. Protenum, oral §	1000	47	37	72	10.8	70	131	36	1149	Mead Johnson
11. Protenum, gastrostomy †	1000	56	53	91	16.5	106	185	52	1575	Mead Johnson
12. Sustagen*	1000	48	35	77	14.6	91	260	13	1500	Mead Johnson
B. JEJUNAL:										
1. Protolysate †	1000	32	85	3	10.5	66	75	0	488	
2. Moore's Formula D §	1000	20	15	20	3.5	21	45	24	470	
C. DRY POWDERED FOOD PRODUCTS, ANALYSIS PER 100 GM. ++										
1. Powdered milk										
2. Dialyzed milk (Lonalac)		21	1	42	4.2	26	39	25	500	Mead Johnson
3. Protenum		20	17	35	6.2	42	46	2	370	Mead Johnson
4. Sustagen		11	11	20	3.7	23	67	3	384	Mead Johnson
5. Protolysate				4	12.4	78	0	0	318	Mead Johnson
6. Dextri-maltose No.2		51	61				100		390	Mead Johnson



\* For support of extracellular fluid and plasma volume in shock due to trauma, hemorrhage, and burns, when parenteral therapy is not available. Prepare by adding 1 heaping teaspoonful (5 gm) of NaCl (table salt) and 1/2 teaspoonful (2.5 gm) NaHCO<sub>3</sub> (baking soda) to 1 quart (960 ml) tap water

+ Mix 125 gm in 900 ml water

# Contains 10 per cent dextrose in 40 per cent vegetable oil

§ Mix 100 gm (2/3 cupful) Protenum with 50 gm (1/3 cupful) Dextri-maltose No.2 (NaCl free) in 910 ml whole milk

‡ Mix 150 gm (1 cupful) Protenum, 75 gm (1/2 cupful) Dextri-maltose No.2, 3 eggs, 2 gm (1/2 teaspoonful) Polyvitamin Dispersion (Mead Johnson), in 820 ml whole milk

★ Mix 390 gm (2 2/3 cupfuls) Sustagen in 780 ml water. May be used for either gastric or jejunal alimentary

† Add 85 gm (1/2 + cupful) Protolysate and 75 gm (1/2 cupful) Dextri-maltose No.2 to 960 ml boiling water  
 § Mix 300 ml evaporated milk, 480 ml lime water, 20 ml Karo syrup, 250 mgm Vitamin C, 8 ml Elixir Feosol, 4 ml B complex, in 200 ml water

++According to analyses in one of our laboratories (J.R.E.)

**1. Water** is naturally taken by mouth or may be given through a tube into the stomach *provided the patient is not vomiting and the stomach is not being drained by suction*. This holds for the sucking of ice as well as the drinking of water. The harm in so doing is the depletion of extracellular electrolyte produced as the result of ionic diffusion across the stomach wall into the salt-free water and its subsequent removal from the body in vomitus or by suction. If under these circumstances fluid must be placed in the stomach for purposes of lavage, isotonic sodium chloride solution should be used. In the conscious patient who can drink water thirst is usually a reliable guide, unless there is a specific reason for limiting the fluid intake. It must not be forgotten, however, that some patients because of weakness or paralysis are unable to respond to the stimulus of thirst. Frequent aid in drinking is required of an attendant.

**2. Sugar solutions** can be given by mouth or tube to supply calories as well as water. Such solution should not be of a concentration of more than ten per cent since more concentrated solutions pull water into the stomach and may lead to vomiting. It should be remembered that lactose and sucrose, especially as admixtures, are more palatable than dextrose.

**3. Carbonated sugar solutions**, such as ginger ale, may appeal more to the taste of the patient. They too should be avoided in the presence of nausea.

**4. Fruit juices** usually are preferable to sugar solutions since they not only taste better but contain potassium and some vitamins as well. The potassium content is high and the sodium content low since they are primarily cellular fluids. The chief exception to this is canned tomato juice which usually has sodium chloride added to it. Fruit juices, because of their high potassium content, are contraindicated in any state of potassium intoxication (e.g., acute renal failure with anuria).

**5. Milk** is a natural food with a high water content and of high nutritional value because of its carbohydrate and protein. The carbohydrate may be fortified with additional lactose or sucrose, as it is in infant formulae. The fat may be removed (skimmed milk) or mixed in (homogenized milk); the latter, of course, contains more calories. Milk is a hypotonic electrolyte solution in which sodium, potassium, chloride, and phosphate predominate.

**6. Dialyzed milk** is available in powdered form under several brand names. It is the residue of milk made sodium-free by dialysis. All the principal electrolytes are so removed but potassium chloride is put back. Hence it is relatively high in chloride and does contain potassium. Such milk has a wide use in the preparation of sodium-free diets for patients with hypertension or various forms of edema. Milk can also be treated with exchange resins to reduce or to alter its electrolyte content for experimental purposes.

**7. Tea and coffee** should also be considered with natural liquid foods.

The leaf and the bean contain potassium but the beverages are essentially electrolyte-free. They do contain caffeine, other alkaloids or acids, and sugar as added. Warm weak tea with sugar is especially acceptable to patients just returning to taking fluids by mouth.

### *B. Gastric*

Intubation of the stomach for prolonged tube feeding is most comfortably accomplished by use of a small polyvinyl tube. Through such a tube, or through a gastrostomy, certain artificial preparations or formulae can be administered as well as the fluid and liquid foods mentioned above. A number of these, shown in table 24-I contain not only water and electrolyte, but also are high in carbohydrate and protein or protein precursors as well. There is also listed a high carbohydrate-high fat-low water formula which is free of potassium and nitrogen. This has been designed for, and used in, the patient with acute renal failure and anuria, described in chapter 12, who should have no potassium or nitrogen, limited amounts of water, and a high caloric intake to spare his own tissue catabolism.

### *C. Small and Large Intestinal*

Composite fluid preparations suitable for instillation into the small intestine through a Miller-Abbott tube or through a tube directly inserted into some portion of the small intestine, are listed in Part B of table 24-I. These are less concentrated than gastric preparations, to avoid distention of the gut. Plain water should not be so placed since it causes necrosis of the ileal mucosa (1).

Water, sodium, and chloride are readily absorbed from the large bowel, but foodstuffs are not. Hence the large intestine is not a good route for administration of constituents other than water and salt, and these are more efficiently given higher up in the gastrointestinal tract or by parenteral routes.

## **III. Intravenous Administration of Parenteral Fluids**

Fluid may be injected into the body by a variety of routes other than the gastrointestinal tract. The intravenous route is currently the most useful though others are also available, including the subcutaneous spaces, the peritoneal cavity, the arteries, and the sternal marrow spaces.

Solutions so given must have certain characteristics: they must be pharmacologically harmless, immunologically inert, and of such osmolar concentrations as not to disrupt erythrocytes by hemolysis or to damage other tissue cells during mixing with the body fluids. The osmolar concentration, however, may vary over a much wider range than in an *in vitro* fluid:red cell system since the injected solution is so rapidly diluted by blood and



body fluids. The ability to maintain fluid balance and nutrition, as well as to correct hazardous abnormalities by the parenteral route when the gastrointestinal tract is not available, is literally lifesaving in many clinical situations. The main types of solutions which are used in parenteral fluid therapy are presented in tables 24-II, 24-III, and 24-IV. These solutions range from the simple to the complex, from those used to repair one fluid compartment or to supply one constituent to those combined to repair several fluid phases and to supply many constituents. Some are widely used routinely, some are designed for special situations. All of these solutions, however, should be used with careful thought for the individual patient's particular requirements, according to the principles which form the basis of this text.

### *A. The Technic of Intravenous Infusion*

This is simple or otherwise according to the accessibility of veins and the skill of the operator. Direct venipuncture with a #19 to #24 needle is most frequently performed on superficial veins in the antecubital space of the arm, the forearm, the back of the hand or foot or around the ankle. In infants the sagittal sinus or external jugular vein may be used. Veins of the limbs that do not stand out are usually made to do so by use of a rubber tourniquet which must be removed of course before the infusion is started. This can be facilitated by rubbing, by opening and closing the hand and by immersing the hand or foot in a warm water bath to produce vasodilation. Where the arm is edematous, application of tight elastic bandages the length of the arm prior to attempting the venipuncture will make the vessels accessible. The extremity is usually best immobilized with a padded board. Due thought should be given to the extreme discomfort to the patient of having the elbow fully extended and forearm supinated. Whenever possible the elbow should be partially flexed and the forearm pronated. If the tip of the needle can lie below the break of the elbow it is less likely to re-puncture the wall of the vein and infiltrate. Use of the veins in the back of the hand is aided by proper padding under the hand and wrist. All needles placed in superficial veins should be firmly taped down and a loop of tubing fastened down with a second piece of tape to prevent pulling out the needle by a sudden motion of the extremity.

Where superficial veins cannot be found or where prolonged infusion is anticipated, a catheter or polyethylene tube can be inserted into a vein through a surgical cutdown. This is most commonly done around the ankle or by intubation of the saphenous vein or of the cephalic vein which permits passing a catheter into the inferior or superior vena cava respectively and so delivering fluid to the central venous system. Such tubes must be kept open by either a slow constant infusion or by filling with a solution of heparin.

### *B. The Rate of Intravenous Infusion*

This should be varied according to the needs of the patient and the type of solution being infused. Blood and colloidal or saline solutions should be given rapidly to a patient in shock, four to eight ml. or 60 to 120 drops per minute, unless the emergency is such as to require intra-arterial injection under pressure. All infusions should be given slowly to patients with cardiovascular disease and actual or potential left ventricular failure. In such patients the lung bases should be carefully examined for rales. Solutions containing potassium should be given slowly, not more than four ml. or 60 drops per minute, to avoid the cardiotoxic effect of too rapid a rise in the extracellular concentration of the ion.

### *C. Hazards of and Contraindications to Intravenous Infusions*

Hazards include any untoward physiologic response to the fluids infused: pyrogenic reaction due to dirty tubing, hemolytic reactions due to mismatched blood or the infusion of pure water without any solute, pharmacologic reactions due to the infusion of solutions containing foreign solutes such as boric acid, pulmonary or peripheral edema due to excessive rates of infusion of fluid (especially those containing sodium), venous thrombosis due to repeated or prolonged infusion in the same vein or to the use of solutions with high concentration of dextrose (20 to 50 per cent), or infection due to contaminated fluids or apparatus. Aside from avoiding these hazards, contraindications to the use of the intravenous route in fluid therapy consist of severe congestive heart failure where no further load should be placed on the right heart, and severe shock where intra-arterial infusion may be necessary to save the patient's life.

### *D. Extracellular Repair Solutions for Parenteral Use*

The salt, ionic, and osmolar compositions of these are presented in table 24-II. In the following discussion each solution, with the exception of the simple ones, is identified by a corresponding letter and number in this table.

*Dextrose solutions* providing water without electrolyte usually consist of the sugar in five or ten per cent concentrations. Water alone cannot be infused because of hemolysis of red cells produced by its hypotonicity. As soon as the dextrose is metabolized or deposited as glycogen the water is freely distributed between the extracellular and intracellular phases. It is, therefore, primarily indicated in the repair of simple dehydration, uncomplicated by electrolyte losses, resulting from insensible water loss in a patient deprived of fluid. Solutions of dextrose in water, therefore, play a major role in the day by day treatment of the patient on parenteral fluids. They have been increasingly used as the hazards of sodium therapy have become appreciated in the postoperative

TABLE 24-II.

PARENTERAL SOLUTIONS I: EXTRACELLULAR REPAIR

TYPE OF SOLUTION	REF.	SALT	CONC. OF SALT Grams%	CONCENTRATION OF IONS							Total mEq./l. mOsm./l	
				Cl <sup>-</sup>	HCO <sub>3</sub> <sup>-</sup>	HPO <sub>4</sub> <sup>=</sup>	Na <sup>+</sup>	K <sup>+</sup>	Ca <sup>++</sup>	Mg <sup>++</sup>		
A. SODIUM CHLORIDE CONTAINING:												
1. "Physiologic" saline		NaCl	0.85	145			145				145	290
2. Hypertonic saline <sup>#</sup>		NaCl	5.0	856			856				856	1721
3. Hypotonic saline plus dextrose <sup>§</sup>		NaCl	0.425	73			73					146
		Dextrose	2.5	73				73			73	126
												272
B. ALKALINIZING, SODIUM CONTAINING:												
1. Hypertonic bicarbonate <sup>‡</sup>		NaHCO <sub>3</sub>	7.5		893		893				893	1786
2. Hypertonic(molar)lactate <sup>†</sup>	2a	NaC <sub>3</sub> H <sub>5</sub> O <sub>3</sub>	11.0		1000		1000				1000	2000
3. Isotonic(1/6 molar)lactate	2a	NaC <sub>3</sub> H <sub>5</sub> O <sub>3</sub>	1.8		160		160				160	320
C. ACIDIFYING, CHLORIDE CONTAINING:												
1. Ammonium chloride	14c	NH <sub>4</sub> Cl	2.0	374							374	748
D. COMBINED EXTRACELLULAR:												
1. Hartmann's saline-lactate	2a	NaCl	0.6	103			103					206
		NaC <sub>3</sub> H <sub>5</sub> O <sub>3</sub>	0.56		51		51					102
		NaCl	0.86	147			147					308
		KCl	0.03	4			4					294
		CaCl <sub>2</sub>	0.033	6			6					8
2. Ringer's		NaCl	0.6	157			157					9
		KCl	0.03	4			4					311
		CaCl <sub>2</sub>	0.022	4			4					206
		NaC <sub>3</sub> H <sub>5</sub> O <sub>3</sub>	0.03	111			111					8
3. Ringer's lactate		NaCl	0.6	103			103					6
		KCl	0.03	4			4					54
		CaCl <sub>2</sub>	0.022	4			4					274
		NaC <sub>3</sub> H <sub>5</sub> O <sub>3</sub>	0.03	111			111					274



4. Sodium lactate calcium gluconate solution for anurics <sup>§</sup>	NaC <sub>3</sub> H <sub>5</sub> O <sub>3</sub> Ca glucon. dextrose	0.9 0.2 10.0	80 9	80	9	160 14 506 640 140 126 34 300 100 176 24 300 200 90 252 542
5. Gastric fluid replacement	NH <sub>4</sub> Cl NaCl KCl	0.375 0.37 0.13	70 63 17	80	9	99
	14d	150	63	63	17	150
6. Intestinal fluid replacement	NaC <sub>3</sub> H <sub>5</sub> O <sub>3</sub> NaCl KCl	0.56 0.51 0.09	88 12	50		150
	14d	100	50	138	12	150
7. Saline-bicarbonate with dextrose <sup>†</sup>	NaCl NaHCO <sub>3</sub> Dextrose	0.595 0.375 5.0	100 45	100		145
		100	45	145		145
PLASMA (extracellular fluid), Ave. normal:		101	27	140	2) <sup>‡</sup>	151
					(5	300

\* Or metabolizable anions, such as lactate or acetate, which are equivalent in their effect on body fluids to adding bicarbonate.

† Commercially available in ampules of 50 ml. containing 45 mEq., should be diluted at least 1.1 with glucose solution.

‡ Commercially available in ampules of 40 ml. containing 40 mEq., should be similarly diluted as in #.

§ Calcium gluconate added to sodium bicarbonate will precipitate. Prepare by adding 2 ampules (20 ml.) of molar sodium lactate and 2 ampules (20 ml.) of 10 per cent calcium gluconate to 900 ml. 10 per cent dextrose in water.

† Mix 500 ml. 0.85 per cent NaCl solution with 500 ml. 5 per cent dextrose in water.

‡ Prepare by adding 300 ml. 5 per cent dextrose containing 1 ampule (50 ml.) of 7.5 per cent NaHCO<sub>3</sub> to 700 ml. 0.85 per cent NaCl solution.

§ 4.25 per cent NaCl solution may be made by diluting ampules of 8.5 per cent NaCl (50 ml. containing 73 mEq.) with equal volume of sterile water.

<sup>‡</sup> Total cation calculated as ionized, although approximately 50 per cent is really bound to plasma protein.

TABLE 24-III.

## PARENTERAL SOLUTIONS II: INTRACELLULAR AND TOTAL FLUID REPAIR

TYPE OF SOLUTION	REF.	SALT	CONC. OF SALT Grams%	CONCENTRATION OF IONS							Total mEq./l. mOsm./l	
				Cl <sup>-</sup>	* HCO <sub>3</sub> <sup>-</sup>	HPO <sub>4</sub> <sup>-</sup>	Na <sup>+</sup>	K <sup>+</sup>	Ca <sup>++</sup>	Mg <sup>++</sup>		
E. POTASSIUM CONTAINING:												
1. Potassium chloride#	5a	KCl Dextrose	0.6 5.0	80				80			160 252 412	
2. Potassium plus sodium chloride§	5a	KCl NaCl	0.6 0.43	80 73			73	80			160 146 306	
3. Potassium phosphate‡	5a	K2HPO4 KH2PO4 Dextrose	0.46 0.1 5.0			53 7		53 7			80 14 252 346 160	
4. Potassium acetate!		KC2H3O2 Dextrose	0.78 5.0		80			80			252 412	
5. High potassium-low sodium for K defic. with alkalosis&	5a	K2HPO4 KH2PO4 KCl NaCl	3.2 0.7 3.0 4.2			37 5		37 5 40			56 10 80 144 290	
				40 72			72				154	

## F. COMBINED ELECTROLYTE

1. Darrow's for acidosis	6a, f	KCl	0.27	35	35	70
		NaCl	0.40	69	69	138
		NaC <sub>3</sub> H <sub>5</sub> O <sub>3</sub>	0.44	53	53	106
2. Butler's for acidosis	6c				157	314
		KCl	0.09	12	12	24
		K <sub>2</sub> HPO <sub>4</sub>	0.03	3	3	5
		NaCl	0.06	10	10	20
3. Butler's multiple electrolyte <sup>†</sup>	6d	NaC <sub>3</sub> H <sub>5</sub> O <sub>3</sub>	0.22	20	20	40
		KCl	0.1	13	13	89
		K <sub>2</sub> HPO <sub>4</sub>	0.1	11	11	26
		NaC <sub>3</sub> H <sub>5</sub> O <sub>3</sub>	0.28	25	25	17
		NaCl	0.17	29	29	50
		NaH <sub>2</sub> PO <sub>4</sub>	0.014	1	1	58
		MgCl <sub>2</sub>	0.025	5	5	2
4. Talbot's multiple electrolyte	6e	Dextrose	5.0			8
		NaCl	0.117	20	20	252
		NaC <sub>3</sub> H <sub>5</sub> O <sub>3</sub>	0.224	20	20	413
		KCl	0.150	20	20	40
		K <sub>2</sub> HPO <sub>4</sub>	0.135	15.5	15.5	40
					75.5	23
						163

\* Or metabolizable anions such as lactate or acetate, which are equivalent in their effect on body fluids to adding bicarbonate.

† May be prepared by adding 2 ampules KCl (each 20 ml. containing 40 mEq.) (commercially available) to 1 liter of 5 per cent dextrose in water.

‡ May be prepared either by mixing 500 ml. of 0.6 per cent KCl with 500 ml. of 0.85 per cent NaCl, or by adding 2 ampules KCl (each 20 ml. containing 40 mEq.) to 1 liter of "half-strength saline" (0.425 per cent NaCl).

§ Add 1 ampule buffered potassium phosphate (20 ml. containing 60 mEq.) to 1 liter of 5 per cent dextrose solution.

|| Add 2 ampules potassium acetate (each 20 ml. containing 40 mEq.) to 1 liter of 5 per cent dextrose in water.

¶ May be approximated by adding 1 ampule buffered potassium phosphate (60 mEq.) and 2 ampules KCl (each 40 mEq.) to 1 liter of 0.85 per cent NaCl mixed with 1 liter of 5 per cent dextrose in water.

• Mg and PO<sub>4</sub> salts must be autoclaved separately to prevent precipitation.



TABLE 24-IV.

PARENTERAL SOLUTIONS III: NUTRITIONAL, AND COLLOIDAL OR BLOOD AND PLASMA VOLUME EXPANDERS										
TYPE OF SOLUTION	VOLUME ml.	CONC. OF SOLUTE gm. %	CONTENT OF STATED VOLUME							
			Cl	Na	K	N	Protein equiv.	Carbo- hydrate	Fat	Calories
			(mEq.)	(mEq.)	(mEq.)	(gm.)	(gm.)	(gm.)	(gm.)	
G. CARBOHYDRATE CONTAINING:										
1. Dextrose in water	1000	5.0						50	200	
2. Dextrose " " "	1000	10.0						100	400	
3. Dextrose " " "	50	50.0						25	100	
4. Invert sugar	1000	10.0						100	400	
5. Fructose	1000	10.0						100	400	
H. PROTEIN PRECURSORS:										
1. Amigeno in 5% dextrose	1000	5.0	19	50	2	6.2	39	50	355	
2. Amigeno in 10% " "	1000	10.0	38	100	4	12.2	78	100	710	
I. COLLOIDAL OR BLOOD AND PLASMA VOLUME EXPANDERS:										
1. Whole blood*	500		13	5	20	11.5	72			
2. Packed red cells*	250		25	38	1	2.8	18		72	
3. Plasma*	250		2	16		4.0	25		100	
4. Conc. Na-poor albumin	100									
5. Gelatin (Knox)	250									
6. Dextran	250									
7. Polyvinylpyrrolidone	250									
8. Acacia	250									
J. FAT CONTAINING:										
1. Fat emulsion (7a,b)	1000	15.0								
							150		1350	

\* Citrated

patient and the patient with edema or hypertension. So much so that it is necessary to warn against the danger of the use of dextrose solutions alone in patients depleted of sodium as well as water with the attendant peripheral vascular collapse and renal failure. In such a patient re-expansion of plasma and extracellular volume with glucose in water alone does not correct the hemodynamic failure. Figures 24-1 and 7-1 to 7-4 illustrate salt depletion in experimental animals and in man, showing the profound circulatory collapse which ensues. Figure 7-4 also indicates that glucose solutions in water must not be given to patients with salt depletion.

*Isotonic sodium chloride* ("physiologic" or "normal" saline) solution (A,1) is isotonic with extracellular fluid only in respect to sodium. The chloride is relatively high. Use of this solution where there is no relative deficit of chloride and where the kidneys are unable to excrete the excess chloride will lead to a hyperchloremic metabolic acidosis. This solution, however, has been the mainstay of parenteral fluid for many years, and, when renal regulation can take place, is invaluable for the repair of prior or concurrent losses of extracellular fluid, e.g., gastrointestinal fluid loss, diabetic ketosis, adrenocortical insufficiency.

*Hypertonic sodium chloride* (A,2) may be given as a two to five per cent solution. It is indicated when there is salt depletion present with a severe deficit of

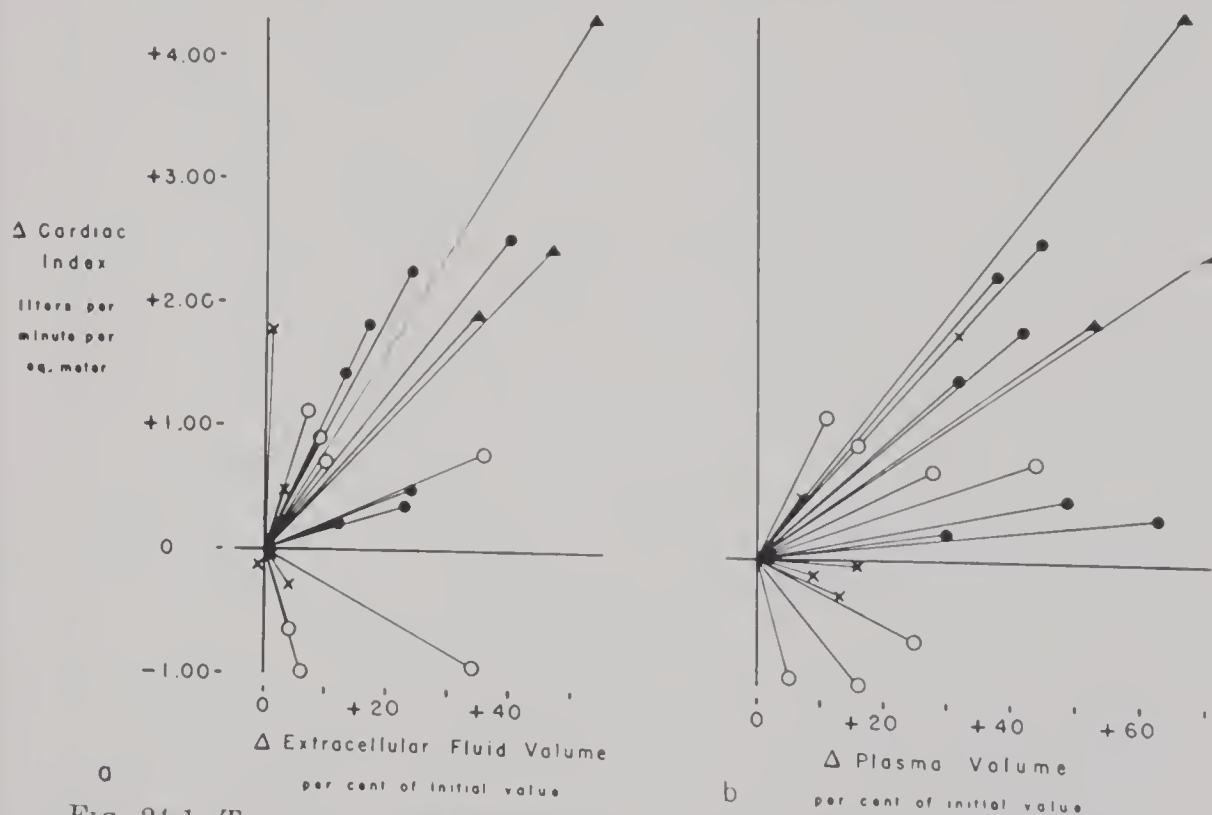


FIG. 24-1. THERAPY OF EXPERIMENTAL SALT DEPLETION SHOCK IN DOGS

Crosses identify untreated controls; solid circles represent animals treated with hypertonic saline and solid triangles those receiving isotonic saline; the open circles identify animals treated with 5 per cent glucose in water.

Although the extracellular fluid volume and the plasma volume expanded in all of the experiments, the cardiac output decreased further in 3 of the glucose experiments. (From Danowski *et al.* (14a).)

extracellular solute in relation to water as evidenced by hyponatremia and hypochloremia. However, hyponatremia with metabolic acidosis, as in uremia, is better treated with hypertonic sodium bicarbonate or lactate. The amount of sodium necessary to restore the concentration to normal may be calculated from the estimated volume of total body water, chapter 3 or 4, but because of the cellular dehydration produced by these solutions only part of this estimated amount should be given in any one 24-hour period. If the object is to raise the sodium concentration, concurrent water restriction must be enforced to not much more than the expected insensible loss by vaporization. The administration of dextrose in water or the drinking of water immediately following the infusion of hypertonic sodium chloride solution obviously nullifies its specific concentrating effect. In patients who can take fluids orally the same effect can be obtained more efficiently by the ingestion of dry sodium chloride as enteric coated tablets each weighing 0.3 gram and providing five milliequivalents of sodium.

*Hypotonic sodium chloride in dextrose* (A,3) is a useful solution for providing a maintenance dose of salt for urinary excretion with extra water for vaporization. It is also a solution that may be safely used for subcutaneous injection.

*Alkalinizing solutions* are those containing sodium as the cation with bicarbonate or with metabolizable anions such as lactate or acetate. The latter are equivalent to bicarbonate in their effect on the body fluids but provide calories as well. These solutions are indicated in metabolic acidosis (diabetic ketosis, infant diarrhea, renal insufficiency). As indicated in chapter 11 part or all of the sodium so administered may enter cells. *Hypertonic sodium bicarbonate* (B,1) and *hypertonic sodium lactate* (B,2) must be diluted with equal volumes or more of water before administration to an acidotic patient whose water requirement is restricted. *Isotonic* ( $\frac{1}{6}$  molar) *sodium lactate* (B,3), or sodium bicarbonate similarly diluted, is useful in such acidotic patients whose water requirements are more normal but whose extracellular sodium is low in relation to chloride.

*Acidifying solutions* are represented in table 24-II only by *ammonium chloride* (C). This solution has been used in patients with severe metabolic alkalosis where only chloride is needed and the linked cation must be disposable or metabolizable. The ammonium ion is converted to urea by the liver, hence this solution is contraindicated in any condition likely to be characterized by a high level of ammonia in the body fluids (liver disease, ? uremia). The metabolic alkalosis due to abrupt and excessive loss of hydrochloric acid in gastric fluid is one clinical situation that could be treated with ammonium chloride. However, most of these patients and most instances of metabolic alkalosis are best treated with solutions containing potassium and sodium chloride (see below, Solutions E,2 and E,5), because of the associated deficits of these cations which develop as described in chapter 6. However, in the occasional case of hypochloremic metabolic alkalosis where the cations, sodium, potassium, and ammonium are contraindicated, hydrochloric acid (with 5 per cent glucose) may be infused in concentrations of 10 to 50 mEq. per liter (0.01 to 0.05 N), (see fig. 23-2).



"Combined" solutions have been designed in a variety of forms to repair deficits of more than one or two principal constituents of the extracellular fluid (2a-c). *Hartmann's saline-lactate (D,1)* was advocated to provide sodium in excess of chloride with a metabolizable anion in a ratio approximating that in true extracellular fluid. This solution, or the readily prepared *saline-bicarbonate with dextrose (D,7)*, is ideal for replacing a deficit of extracellular fluid not characterized by any marked relative ion (acid:base) disturbance (2a-c). It places no stress on the kidney to make a cation-anion adjustment. *Ringer's solution (D,2)* is predominantly a sodium chloride solution modified to provide concentrations of potassium and calcium at levels corresponding to those in the extracellular fluid. *Ringer's lactate (D,3)* more nearly approximates the physiologic extracellular fluid in that the lactate is equivalent to bicarbonate and thus the sodium exceeds the chloride. This is an ideal *in vitro* perfusion fluid for organs and tissues, but, in the authors' opinion, is seldom required in clinical fluid therapy since in any condition associated with loss of potassium, cellular deficits of this ion occur. Such situations require the administration of potassium in amounts much larger than the homeopathic dose provided in Ringer's solutions. The *sodium lactate-calcium gluconate-dextrose solution (D,4)* is one frequently used by the authors in the treatment of the anuric patient. This solution provides sodium with a metabolizable anion to combat hyponatremia, extracellular metabolic acidosis, and intracellular sodium deficit. The calcium is important for two reasons: 1) the concentration of this ion is frequently depressed in such cases in association with the hyperphosphatemia, and 2) the shift of pH in the alkaline direction due to the sodium lactate may induce tetany. The simultaneous administration of calcium prevents this. Dextrose in ten per cent solution provides calories to spare tissue catabolism, and the total water volume is limited, as is so necessary in these cases. This solution is easily modified to meet day by day circumstances: less or more sodium according to the clinical and biochemical indication, more calcium if tetany or convulsions ensue or if potassium cardiotoxicity is to be combatted by giving calcium, and more or less water as the weight changes or the onset of pulmonary edema may indicate.

Two solutions are presented which are designed specifically for *gastric fluid replacement (D,5)* and for *intestinal fluid replacement (D,6)*. The former provides chloride in excess of sodium (the ammonium in the  $\text{NH}_4\text{Cl}$  is disposable in that it is converted to urea), and potassium, in concentrations approximating those in normal gastric fluid. The latter provides an alkaline (sodium in excess of chloride) solution, with potassium, in concentrations similar to those in *succus entericus*. Both of these solutions are especially useful in replacing measured losses from the gastrointestinal tract.

### *E. Intracellular and Total Fluid Repair Solutions*

These are presented in table 24-III. Most of these solutions contain electrolytes that are present in extracellular as well as intracellular fluid. But the first group of solutions are those primarily containing potassium and are intended to provide adequate amounts of this major intracellular

cation. A number of combined or multiple electrolyte solutions have also been designed to provide repair of both intracellular and extracellular fluids.

*Potassium chloride (E,1)* is the potassium salt most frequently used in parenteral therapy. It may be combined with extracellular salt, *potassium plus sodium chloride (E,2)*, where deficits of extracellular fluid are involved. Where intracellular cation deficits predominate, however, it is preferable to use the potassium without the sodium salt since there is considerable experimental evidence that the administration of sodium ion aggravates intracellular potassium deficiency (3a, b) (see fig. 7-10). It is interesting that this is in keeping with Bunge's original observation (3c, d). It is desirable, whenever possible, to give dextrose with potassium because of the association of cellular uptake of potassium with the utilization of carbohydrate (4a-c).

Potassium chloride has been given parenterally in "isotonic" concentration of 150 milliequivalents per liter by some workers, but in the opinion of the authors it is potentially hazardous to give such high concentrations to any but the most severely depleted patients.

*Potassium phosphate (E,3)*, buffered amounts of the dibasic and monobasic salts, provides intracellular anion as well as cation. This is a logical solution to use in straight intracellular deficiency without associated metabolic alkalosis, e.g., starvation, diabetic ketosis, although no evidence has been adduced to show that provision of the intracellular anion facilitates uptake of the cation.

*Potassium acetate (E,4)* provides intracellular cation with a metabolizable anion. This combination is indicated in those situations where potassium deficiency is associated with a metabolic acidosis due to retention of "fixed" anions such as chloride or phosphate, e.g., renal tubular acidosis with hyperchloremia, potassium wasting chronic renal insufficiency with phosphate retention, or more acute renal failure due to circulatory insufficiency in potassium depleted patients. In this last category of patients it is usually wise to restore the circulation with extracellular solution before attempting treatment with potassium.

The *high potassium-low sodium solution (E,5)* was designed by one of the authors, J. R. E. (5a, b), for treatment of the specific condition of extracellular metabolic alkalosis associated with intracellular potassium deficiency, as described by Darrow *et al.* (5c-e). The administration of potassium to such patients leads to a large transfer of sodium from cells to extracellular fluid. The provision of more chloride than sodium allows for this transfer. Intracellular anion, phosphate, is provided but the intracellular cation, potassium, is given in larger amounts to exchange for the cellular sodium. This is an ideal solution. The same net effect can be accomplished with potassium chloride, sodium chloride solution (5f, g), in the presence of adequate renal function.

*Darrow's solution (F,1)* provides an isotonic mixture of sodium chloride and sodium lactate with potassium chloride, a solution that he has found useful in the treatment of severe infant diarrhea with both extracellular metabolic acidosis and intracellular potassium deficiency (6a, b).

*Butler's solution (F,2)* has been used for treating the same condition and for



diabetic acidosis (6c). It differs from Darrow's in that the potassium is somewhat less concentrated, some phosphate is included, and the total solution is hypotonic, 89 compared to 300 milliosmols per liter, to provide free water for vaporization.

*Butler's multiple electrolyte solution (F,3)* is likewise hypotonic for the same reason in respect to electrolyte, and provides with the exception of calcium all of the principal extracellular and intracellular ions (6d). It also includes magnesium. This solution is especially useful in treating diabetic coma.

*Talbot's multiple electrolyte solution (F,4)* is somewhat simpler in that it contains no magnesium. It has been promulgated as an "all purpose" solution which will improve the patient no matter what his original deficiencies might be. This solution provides free water and is recommended in a dosage of about 3 liters per square meter of body surface per day (6e). The principal advantage hoped for from this preparation is that the stressed patient's homeostatic limits will never be exceeded (chapter 23). Routine use of this solution, however, may not be the best treatment in the patient with severe impairment of his regulatory mechanisms, especially in renal failure, or with marked abnormality of certain constituents of his body fluids, e.g., potassium deficiency or edema; water is for example a real risk in patients with inability to excrete excess water (6f). Nevertheless, the intelligent use of this solution should go far in eliminating the excesses and iatrogenic stresses which not infrequently result from unthinking fluid therapy.

#### *F. Parenteral Solutions to Meet Nutritional and Caloric Requirements*

These are presented in table 24-IV. These are subdivided into those providing carbohydrate and those providing protein precursors. The intravenous infusion of fat preparations is still in the experimental stage. The 15 per cent emulsion used by Stare *et al.* (7a, b) is listed at the end of this table (J,1).

*Dextrose solutions* may be given as five per cent solution (G,1), which is essentially isotonic or iso-osmolar, or as ten per cent solution (G,2). The 50 per cent solution (G,3) may be injected intravenously but may cause venous thrombosis. Fructose solutions have recently been advocated for parenteral fluid therapy. Since this sugar is not excreted as rapidly as dextrose, it provides more calories per gram infused and has the added advantage that insulin is not required for that portion which succeeds in entering the glycolytic cycle directly. It has been recommended by some for use in the early treatment of diabetic ketosis and coma (8a-i).

The availability of *casein hydrolysates* or protein precursors for intravenous infusion has greatly enhanced the physician's ability to maintain the patient's nutritional status and to combat tissue wasting. Such preparations are given as five per cent (H,1) or ten per cent (H,2) solutions and are best combined with carbohydrate to spare protein catabolism. Six to 12 grams of nitrogen, equivalent to 39 to 78 grams of protein per liter of solution, can be administered



in this way. Such doses go a long way toward maintaining nitrogen equilibrium in the average patient, but interfere with appetite if given during the day (9a-c).

### G. Intravenous Solutions to Expand the Blood and Plasma Volume

These constitute a very important category of therapeutic tools in clinical medicine. The principal types are presented in table 24-IV.

*Whole blood (I,1)* is still considered the best treatment for peripheral vascular collapse or shock due to hemorrhage, trauma, burns. It also provides red cells for oxygen transport. It is especially indicated, therefore, in severe anemia or hemorrhage.

*Packed red cells (I,2)* are used where the patient is anemic but has evidence of vascular engorgement, i.e., has a low total red cell mass but a high absolute as well as relative plasma volume, e.g., congestive heart failure with anemia.

*Pooled plasma (I,3)* is frequently used as a physiologic plasma expander. It is indicated in any condition of shock but especially in those due to loss of plasma alone, as in severe burns. Its advantage consists chiefly of the speed with which it can be used because typing can be omitted and crossmatching is greatly simplified or unnecessary. Its chief disadvantage is that the virus of viral hepatitis may be transmitted. Fresh plasma may also be required to provide certain factors necessary for blood coagulation (e.g. a-c globulin) in certain blood dyscrasias.

*Concentrated salt-poor albumin (I,4)* is useful in those conditions where a deficiency of plasma protein is contributing to edema, e.g., ascites, nephrosis.

*Gelatin (I,5)* was one of the first of the artificial plasma expanders. It shares with the more recent ones, such as *Dextran (I, 6)* and *Polyvinylpyrrolidone (PVP) (I,7)*, the slight uncertainty of its effectiveness due to variation in molecular size and hence osmotic (oncotic) properties. Nevertheless, these products are important because of the possibility of stockpiling them in large amounts for use in widespread military or civilian disaster. *Acacia (I,8)* was the earliest of the artificial plasma expanders but has been pretty generally discarded because of the evidence that it is deposited for prolonged periods in the liver and reticulo-endothelial system. This same question has been raised with regard to dextran and polyvinylpyrrolidone without complete resolution (10a-f). In addition prolongation of bleeding time has been reported following dextran (10f, g).

In concluding this section on intravenous fluid therapy it is again pointed out that the choice of the fluids to be administered depends upon the intelligent consideration by the physician of the patient's individual problem. For the vast majority of cases the more complicated solutions are usually not necessary. Simple combinations of water, dextrose, sodium chloride, sodium lactate or bicarbonate or potassium chloride, supplemented by protein hydrolysates and blood or plasma expanders as needed, will suffice.

In any case intravenous fluid administration is one of the major procedures in the whole field of treatment of the body fluids.

In table 24-V some of the available ampules of concentrated electrolytes are listed for ready reference.

#### IV. The Subcutaneous Route for Parenteral Therapy

The administration of crystalloid solutions by hypodermoclysis is practised less frequently than formerly since improved methods have been developed for maintaining a prolonged intravenous infusion. The subcutaneous route, however, does provide a way to give fluid parenterally when a vein cannot be entered and is sometimes indicated when the rapid addition of fluid to the venous system is undesirable, as in severe congestive heart failure.

The number of solutions that can be administered subcutaneously with safety are much fewer than those which can be given intravenously. While a dilute potassium solution such as Darrow's (F,1) can be given in this manner this route is usually used for administering extracellular repair solutions of electrolytes, dextrose, and water. Of these, the two solutions that should be used are 0.85 per cent sodium chloride (A,1) or hypotonic half-strength sodium chloride in dextrose solution (A,3). Five per cent dextrose (G,1) or any solution without extracellular electrolyte in at least one-half isotonic strength should *never be given subcutaneously*. To do so is to produce actual or potential state of shock. This is the hemodynamic effect of sodium depletion as described in chapter 7 and figures 7-1 and 7-2 and is due to the diffusion of extracellular electrolyte into the temporarily sequestered subcutaneous depot of dextrose solution. The procedure is the counterpart of Darrow's report of the experimental production of sodium depletion by intraperitoneal infusion of dextrose solution (11a). Dextrose hypodermoclyses have been shown by the authors (11b, c) to produce the same effect in human subjects (fig. 7-4). This observation has subsequently been confirmed by others (11d). An opposite or dehydrating effect also may be produced by the subcutaneous injection of hypertonic or hyperosmolar solutions, such as three or five per cent sodium chloride or 0.85 per cent sodium chloride combined with five per cent dextrose (11e, f).

Recently it has been found that the addition of the enzyme, hyaluronidase, to fluids given by this route will facilitate their spread through the subcutaneous tissues and hasten absorption (12a, b). This diminishes the discomfort to the patient. There is no evidence that it increases the shock-producing property of hypotonic electrolyte solutions when given by this route, despite interpretations to the contrary, but neither is this cancelled (12b-d). Hence the enzyme is best used with solutions which contain sodium.

TABLE 24-V.

CONCENTRATED SOLUTIONS OF SALTS IN STERILE AMPULES FOR PREPARING PARENTERAL FLUIDS									
SOLUTION NO.	SALT	CONC. (gms.%)	H <sub>2</sub> O (ml.)	AMPULE CONTENT					
				Cl <sup>-</sup> (meq.)	HCO <sub>3</sub> <sup>-*</sup> (meq.)	HPO <sub>4</sub> <sup>=</sup> (meq.)	Na <sup>+</sup> (meq.)	K <sup>+</sup> (meq.)	Ca <sup>++</sup> Mg <sup>++</sup> (meq.) (meq.)
1.	NaHCO <sub>3</sub>	7.5	50		45		45		Abbott
2.	NaC <sub>3</sub> H <sub>5</sub> O <sub>3</sub>	11.0	40		40		40		Lilly
3.	NaCl	8.5	50	73			73		
4.	KCl	14.85	20	40				40	{ Lilly Abbott
5.	K <sub>2</sub> HPO <sub>4</sub> + ) KH <sub>2</sub> PO <sub>4</sub>	23.0 5.0	20			60		60	Abbott
6.	KC <sub>2</sub> H <sub>3</sub> O <sub>2</sub>	19.6	20		40			40	
7.	Ca gluconate	10.0	10		4.7			4.7	Abbott
8.	MgSO <sub>4</sub>	10.0	20						Lilly
9.	Dextrose	50.0	50						Abbott

\* Or metabolizable anion equivalent to bicarbonate in its effect on the body fluids



## V. Administration of Fluids via the Peritoneal Cavity

This route can be used for the administration of the same solutions as may be given by hypodermoclysis. The same hazards obtain, however, and in addition there is the possibility of peritonitis due to contamination of the needle or of the solution. For this reason this route is seldom used at present despite the advent of antibiotics.

## VI. Intra-arterial Fluid Therapy

The infusion of fluid into the arterial circulation must be done under a hydrostatic pressure exceeding that of the arterial systolic pressure. This route, therefore, is generally used under conditions of urgency for rapid restoration of blood volume and pressure on the arterial side of the circulation, e.g., severe hemorrhage such as may occur during cardiac surgery. Hence, the solutions given in this way are usually whole blood, plasma, or plasma expanders. Under conditions of shock intra-arterial infusion may have definite advantages over the intravenous route, but care must be used to avoid potassium intoxication (13a, b).

## VII. Fluid Redistribution as a Clinical Problem

As indicated in chapter 8 abnormalities in the regional distribution of fluids sometimes occur, as well as total deficits or excesses of particular constituents. Such alterations in distribution are usually the consequence of circulatory inadequacy, since transport and homogeneity of fluid within the body depends primarily upon the circulation or the "mixing apparatus." Therapeutic measures, therefore, which affect body fluid redistribution rather than the external exchanges, are for the most part measures designed to improve the circulation.

### A. Circulation

**1. Peripheral factors** of the circulation that may be improved are many. a) Change in position will alter the venous hydrostatic pressure and so shift the distribution of edema fluid. This is often seen when the cardiac with edema of the lower legs goes to bed. The edema shifts to the hip area and not infrequently a diuresis sets in without further treatment. b) Removal of obstruction to the venous return in any region of the body will mitigate edema due to that cause. c) Improvement of the peripheral arterial circulation, in states of actual or incipient shock, with transfusions or with nor-epinephrine will often help to mobilize edema.

**2. Central circulatory failure of the heart** is often a factor in disorders of fluid distribution. This should always be in the mind of the physician since adequate cardiac function is a *sine qua non* to a healthy state of the

body fluids. a) Digitalization is the most important therapeutic measure in this respect and should always be attempted, unless specially contraindicated, whenever heart failure is suspected as a factor in the fluid disturbance. b) Quinidine and other drugs should be used as specifically indicated. c) Oxygen in the cyanotic or anoxic patient is helpful.

### *B Other Factors*

Aside from the circulation *per se* a few other factors should be briefly mentioned. a) External hydrostatic pressure can be used to prevent or to shift edema of an extremity by binding with an elastic roll bandage, e.g., burns, postsympathectomy vasodilatation in legs. b) Enzymes other than hyaluronidase, cited earlier, have been used to increase the mobility of fluids in certain parts of the body, e.g., *streptodornase* in pleural spaces.

**SUMMARY:** In most illnesses without antecedent deficits and with intact circulating, regulating, and renal mechanisms, oral or parenteral fluid therapy is simple and consists of a) prescription of calories and perhaps nitrogen in the form of glucose and amino acids, b) adequate replacement of the water lost in urine and in insensible and sensible perspiration, c) minimal provision of sodium chloride, zero to several grams per day, relying upon the renal conservation of these ions during periods of reduced intake, and d) administration of potassium in amounts sufficient to replace losses. With prolonged illnesses or with disturbances in the volume, composition, and distribution of the body fluids special solutions must be used. These are designed to permit safe and effective correction of such disturbances. These are usually given by vein. If the subcutaneous route is employed the hazard of producing salt depletion by means of non-electrolyte solutions must be kept in mind.

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## *Chapter 25*

### **VIVODIALYSIS IN THE THERAPY OF EXCESSES OR DEFICITS**

In the preceding chapter the use of solutions in the repair of disturbances of body fluid composition has been discussed with especial emphasis upon the cancellation of deficits. In this chapter the technics of vivodialysis will be reviewed. Dialysis may be defined as separation of solutes by differential diffusibility through a porous membrane or barrier placed between two solutions. This differential diffusibility may be readily produced by establishing concentration gradients between the two solutions involved (fig. 25-1). Membranes through which dialysis can be performed may be natural or artificial; the former consist of the wall of the gastrointestinal tract or the peritoneum, the latter of cellophane placed between the patient's circulating blood and the dialyzing solution.

In the sections which follow the role of vivodialysis in the removal of excesses of body solutes or water, supplementing or replacing diuretics, cation exchange resins, and the other procedures already discussed in chapter 9, will be indicated. It should be kept in mind however that by appropriate selection of the dialyzing fluid these maneuvers, i.e., gastrointestinal or peritoneal lavage or application of an artificial kidney, can also be employed to cancel deficits. However, this is readily accomplished only by the last of these procedures.

#### **I. Gastrointestinal Dialysis**

The gastrointestinal tract has been used for this purpose in several different ways: by ingestion of large volumes of water and purging to produce an excessive diarrhea, by gastric lavage and vomiting, and by perfusion of the small intestine through a double lumen Miller-Abbott tube. This latter method is the preferable technic since exchanges of solutes can be more easily controlled (1a-j).

The dialyzing solution of choice for this method is a two per cent solution of sodium sulfate. Solutions of sodium chloride or bicarbonate are usually absorbed even against a concentration gradient whereas divalent ions are not. The use of sodium chloride or similar univalent ion solutions, therefore, even in hypertonic concentration, leads to a hazardous state of edema whereas sodium sulfate does not have this effect. Sucrose or dextrose solutions on the other hand may lead to overhydration or sodium depletion. With any of these solutions depletion of potassium with hypokalemia should be watched for.

The rate of perfusion recommended by some workers is one to two liters per hour for periods ranging from eight hours to four days. However the rate and duration in any individual instance should be determined by the progress of the patient. The amount of urea reported to have been removed in this manner has ranged up to 69 grams over several days (1a-j).

Undoubtedly this is an effective procedure in uremics. The principal difficulty in our hands has been in effecting the passage of the tube through

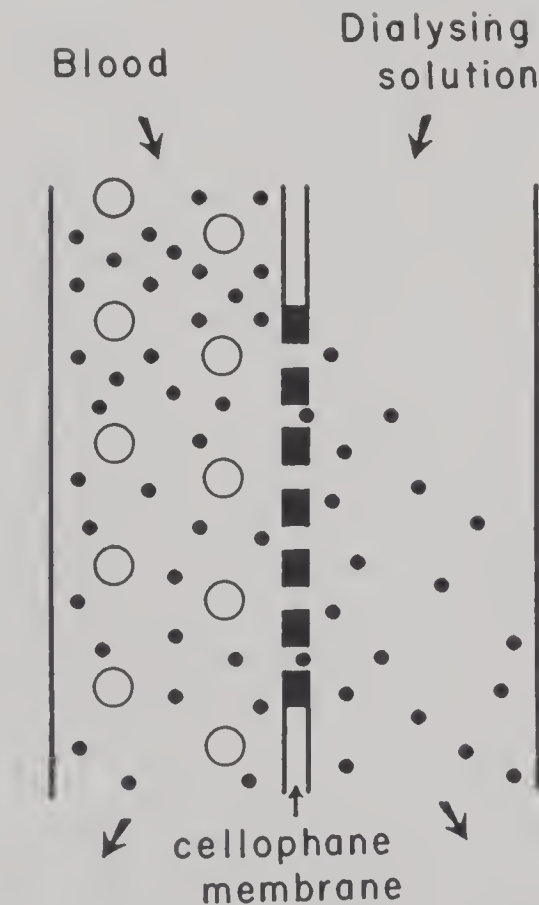


FIG. 25-1. PRINCIPLE OF DIALYSIS ACROSS A CELLOPHANE MEMBRANE

The large open circles on left represent red cells and protein molecules which are too large to pass through the pores of the cellophane membrane. The small solid circles indicate solutes which are small enough to pass through the membrane and hence move down concentration gradients (from left to right). Other diffusible solutes present in equal concentrations on both sides effect no net transfer and are not shown.

the pylorus in uremic patients who are usually nauseated. However, the advantages of this method of dialysis lie in the availability of the intestinal tract, as compared to the artificial kidney, and the minimal danger of infection due to contamination of apparatus and solutions.

## II. Peritoneal Dialysis

Lavage of the peritoneal cavity was early demonstrated to be a therapeutic dialyzing procedure by Rhoads, by Fine, Seligman and coworkers, and by others (2a-j). More recently it has been advocated by Muirhead (2k-o) and Grollman (2p). Dialyzing solutions must be essentially of extracellular fluid composition (sodium, chloride, and bicarbonate), with a pH close to 7.4, must be sterile, and should be warmed to body temperature. The complications consist of losses of protein, overhydration and edema, peritonitis, and interruption of the perfusion channels by the omentum. For these reasons this method of dialysis seems at present less desirable than gastrointestinal perfusion or extracorporeal vivodialysis (artificial kidney), and has not been used by the authors.

## III. Extracorporeal Hemodialysis by Means of an Artificial Kidney

### A. Development and Types

The first attempt to use an artificial membrane for the dialysis of blood outside the body was that of Abel, Rowntree and Turner (3a) in 1913. These workers shunted the blood of experimental animals through collodion tubes which were bathed in hypotonic sodium chloride solution, and demonstrated the outward diffusion of nonprotein nitrogen and substances such as salicylates. Since then other types of membranes have been used (3b-e) but the principal limitations lay in the inadequacy of methods for anticoagulation of the blood and sterilization of the membrane. The advent of heparin and cellophane, however, first used by Thalhimer (3f, g), made practicable the clinical use of extracorporeal dialysis.

Kolff was the first to successfully apply this technic to the treatment of a series of patients (4a-c). His apparatus consists of cellophane tubing wound around a drum which revolves in a bath of dialyzing solution (fig. 25-2). Since the tubing is distensible, the transfer of water between blood and dialyzing solution must be regulated by adding glucose to the latter in just the right concentration to oppose the oncotic pressure of the plasma protein. This apparatus with modifications has been employed by Merrill and associates (4d-h) and others (4i-m), and is the most commonly used type of artificial kidney at present. Alwall and Murray have developed artificial kidneys which differ from Kolff's in that the cellophane tubing is supported in a semirigid position by wire screening (5a-d). An Alwall type kidney as constructed by Barker and Jernstedt of the Westinghouse Com-



pany has been used by one of the authors (T. S. D.) and his colleagues (5e, f). Skeggs and Leonards (5g, h), by abandoning cellophane tubing and using sheets of cellophane between grooved rubber pads, achieved a completely rigid apparatus in which manipulation of the hydrostatic pressure gradient permits efficient ultrafiltration as well as dialysis. This is the artificial kidney used by the other author (J. R. E.) and his colleagues (5i) one of whom, Bluemle, has further modified the apparatus by winding cellophane tubing in a helix of grooved plastic strips thereby combining the advantages of cellophane tubing (Kolff) with complete rigidity of support (Skeggs-Leonards). This is not unlike the new model recently suggested by Kolff. The three types of artificial kidneys are illustrated in figures 25-2, 25-3, 25-4. However, others based on the use of cellophane or exchange resins have also been described (6a-g).

### *B. Efficiency of These Three Types of Dialyzing Units*

The physiologic and biochemical functions of the artificial kidney depend, of course, on the structural characteristics and the conditions of operation of each particular apparatus. Efficiency of dialysis is primarily a function of the concentration gradient which in turn is determined by the rate of blood flow, the thickness and porosity of the cellophane membrane, and its total surface area. It is usually quantitated in terms of the clearance of

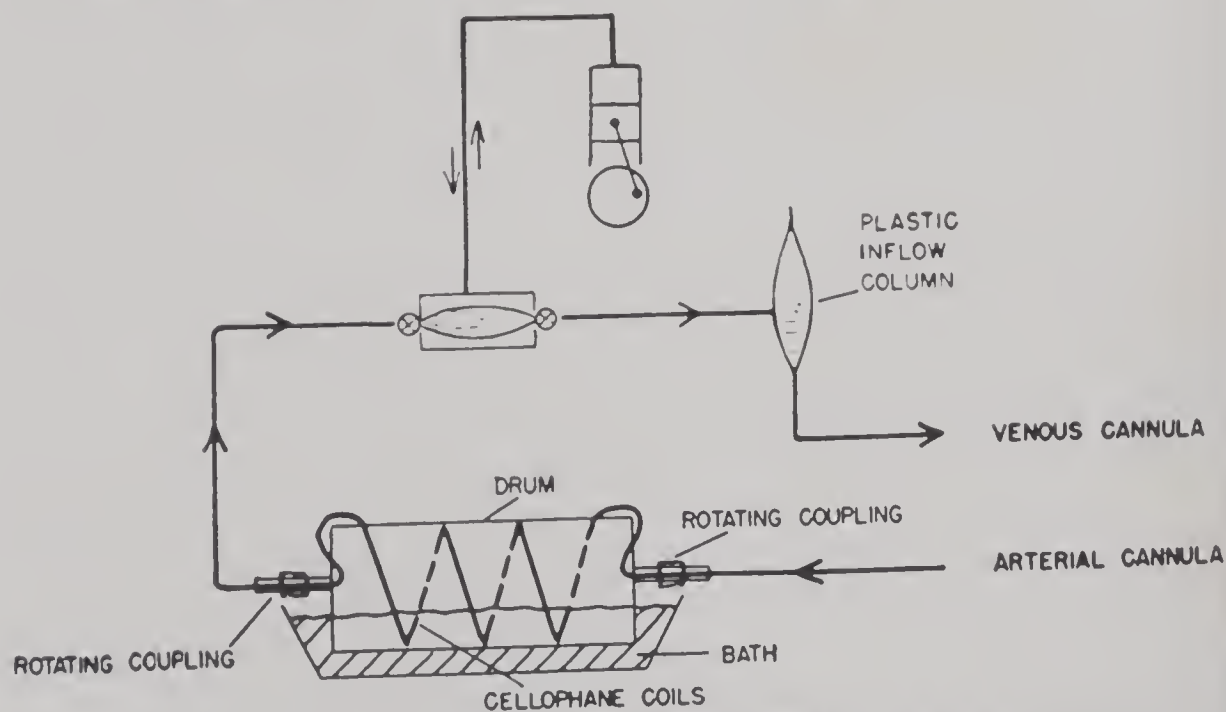


FIG. 25-2. EXTRACORPOREAL DIALYSIS: DIAGRAM OF THE MODIFIED KOLFF ARTIFICIAL KIDNEY

Blood is pumped from the patient through cellophane tubing wound on a revolving drum. Part of the drum is immersed in a large bath of dialyzing solution. (From Merrill *et al* (4d).)

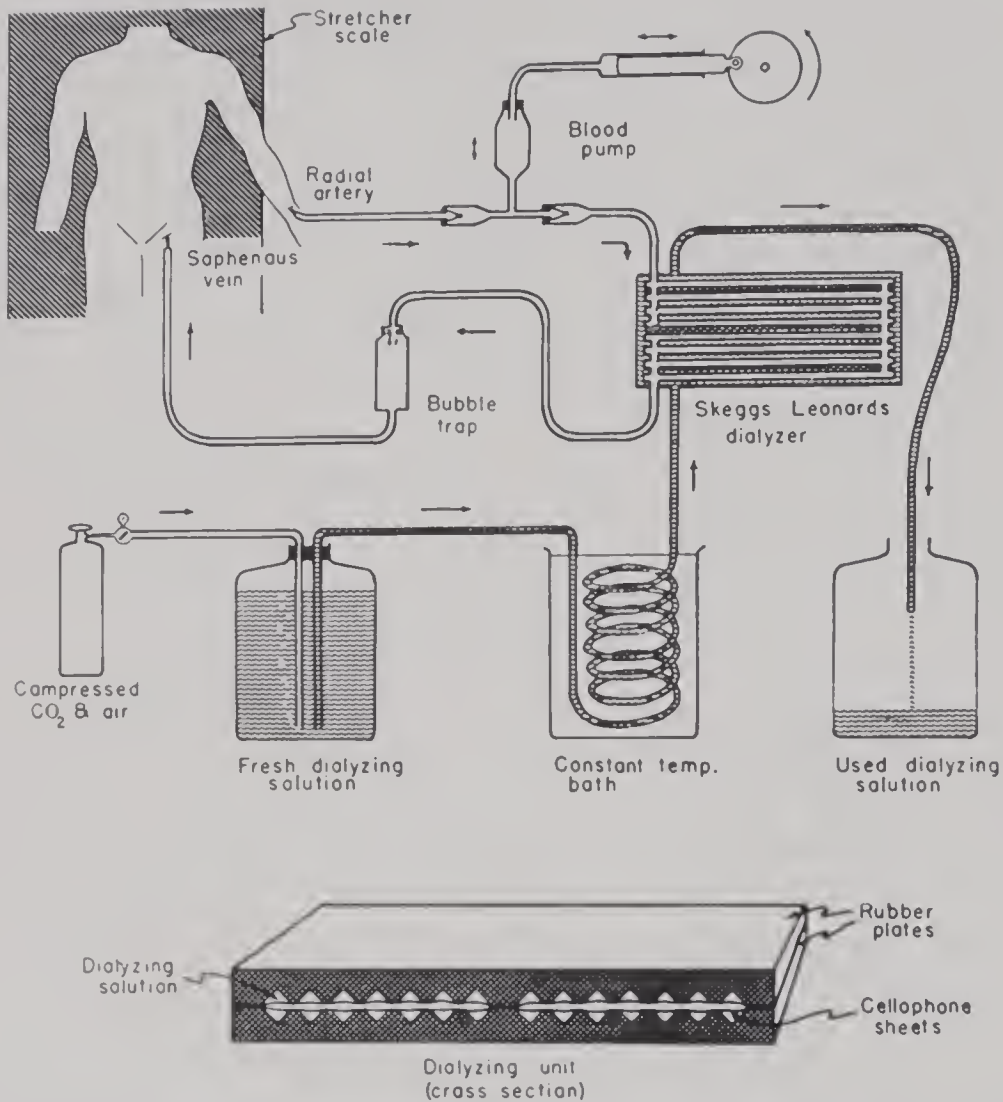


FIG. 25-3. EXTRACORPOREAL DIALYSIS: CIRCUIT OF THE SKEGGS-LEONARDS ARTIFICIAL KIDNEY

Blood flows between two sheets of cellophane rigidly supported by grooved plates; diffusible solutes exchange with the dialyzing solution passing through the grooves. The sets of plates are connected in parallel and then in series. Blood is pumped from the radial artery by positive-negative pressure through the dialyser and back through a bubble trap to the saphenous vein. Dialysing solution is forced by  $\text{CO}_2$  and air pressure through a constant temperature bath into the dialyser and out to a discard carboy; it is not recirculated. Because of the rigid support the apparatus may be used as an ultrafiltrator as well as a dialyser. (From Bluemle, *et al.* (5i).)

urea calculated from the formula  $C = DV/P$  where  $C$  is the ml. of plasma cleared per minute,  $DV$  is the amount of urea removed per minute into the dialyzing solution, and  $P$  is the average concentration of urea in the plasma. Wolf and associates (6h) have suggested the term "dialysance" in their precise characterization of the kinetics of a Kolff-type dialyzer. With blood flows varying between 70 and 300 ml. per minute in the Kolff kidney in which the surface area of the cellophane approximates 24,000  $\text{cm}^2$ ,

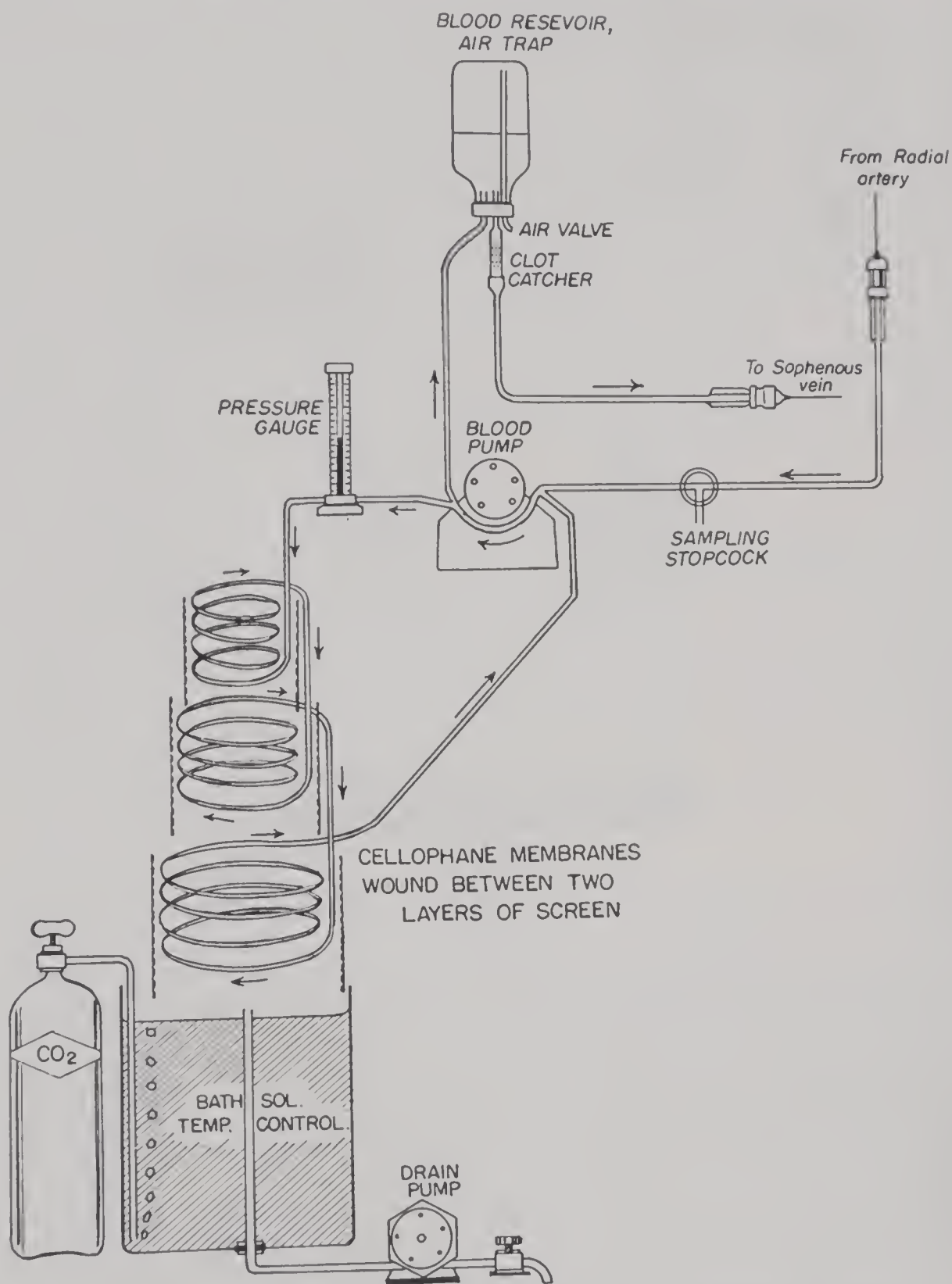


FIG. 25-4. DIAGRAM OF THE WESTINGHOUSE ALWALL ARTIFICIAL KIDNEY

The cellophane tubing is constricted by three sets of concentric perforated cylinders which permit control of the volume and pressure of the extracorporeal blood.



Merrill has reported the urea clearance to vary between 37 and 230 (average 143) ml. per minute (7a). Comparable figures for the Skeggs-Leonards apparatus, (surface area approximately 12,000 cm.<sup>2</sup>) in our hands (J. R. E.), show at a blood flow of 150 to 250 ml. per minute, a urea clearance of ten to 143 ml. per minute with an average of 85 ml. per minute (7b). The Westinghouse-Alwall dialyzer, used by the other author (T. S. D.) has a smaller urea clearance (5e). These clearance values mean that urea can be removed from the severely azotemic patient in amounts of the order of magnitude of 40 to 60 grams in three hours of dialysis with the Kolff kidney, four to six hours with the Skeggs-Leonards apparatus, and longer if the Westinghouse-Alwall unit is employed. It is of interest to realize that at the rate of blood flow of 250 ml. per minute, 15 liters of blood per hour is shunted through the extracorporeal circuit. In three hours this is approximately equivalent to the total body water of an average sized adult.

### *C. Experimental Use*

An artificial kidney provides a unique tool for the experimental manipulation of the body fluids. It has been used to study the hypertensive state (4f, 8a), the presence in blood of pressor or other humoral substances (8b, c), the quantitative interrelationships of changes in certain dimensions of the body fluids (9a-d), and the effect of changing levels of extracellular and intracellular potassium of the heart on the electrocardiographic pattern and on its sensitivity to digitalis (9e, f). In addition the relationships between cellular potassium transfers and acid-base equilibrium in humans and animals with and without intact kidney function have been defined (9g-k). In this last group of experimental studies, the animal has an artificial glomerular function but no renal tubular function, thus permitting differentiation of which ionic transfers are initiated primarily in the peripheral tissue cells and which are initiated in the cells of the renal tubule. Undoubtedly the artificial kidney is currently being put to still other experimental uses.

### *D. Clinical Operation*

The treatment of human patients with an extracorporeal dialyzer or artificial kidney requires a well-trained and well-co-ordinated team which is thoroughly acquainted not only with the mechanical details of the apparatus but also with the complicated factors involved. In the beginning such skill and knowledge should be gained by using the apparatus on experimental animals. Each team must thoroughly master the mechanical details of operation and be able to predict, within a reasonable range, the chief physiological and biochemical results of such operation. For this reason it is unlikely that the therapeutic use of an artificial kidney will be, or should

be, undertaken in other than the larger medical institutions where ancillary scientific facilities are adequate and available.

Some of the problems of operation may be listed as follows: a) The apparatus must be **cleaned and set up** without leaks in the blood or dialyzing solution circuits. b) The apparatus must be **sterilized** on the blood side. c) The apparatus must then be **primed with bank blood** of the correct type; in the Skeggs-Leonards dialyzer and in the Westinghouse-Alwall unit as used in our departments this amounts to 400 to 500 ml. d) **Dialyzing solution must then be prepared** of the correct compositions and in adequate amounts. Directions for the preparation and the composition of the dialyzing solutions used in our Skeggs-Leonards are presented in table 25-I. These solutions are close to interstitial extracellular fluid in ionic composition and hydrogen ion concentration. By using such a dialyzing solution diffusible solutes which are present in abnormally high concentration in the blood move down the concentration gradient *into* the dialyzing solution (e.g., urea, phosphate, potassium, components of the "x" or undetermined acid fraction of the Gamble diagram, or exogenous substances such as salicylates), and those in abnormally low concentration (e.g., sodium or calcium) in the blood are replenished by movement down the concentration gradient *from* the dialyzing solution. e) **Adequate blood flow** from and to the patient must be established. This usually means cannulating the radial artery and inserting a polyethylene tube into the inferior vena cava through the saphenous vein. Both of these procedures require a surgical cutdown, and at the end of the dialysis the vessels must be tied off and the incision properly closed. The patient must be given heparin in the proper priming and maintenance doses to produce adequate but not excessive anticoagulation. This is judged by previous experience or by measuring at intervals the coagulation time of blood samples taken from the afferent blood stream in the apparatus. At the end of the dialysis the effect of the heparin is nullified by an injection of protamine (10a, b).

The effect of dialysis on the concentration of blood urea-nitrogen in acute renal failure is shown in figure 25-5. The effect on other abnormalities in concentration and in acid-base equilibrium, on the same patient, is shown in figure 25-6. The correction of the metabolic acidosis by the dialytic removal of retained undetermined acids, phosphate, and sulfate, and excess potassium in the extracellular fluid are probably more important for the physiologic welfare of the severely uremic patient than is the removal of urea, but all of these corrections depend upon the efficiency of the artificial kidney as a dialyzer.

Ultrafiltration by the artificial kidney is possible only in those apparatuses with rigid support of the cellophane (e.g., Alwall, Skeggs-Leonards). This process may be defined as the mass movement of fluid, solvent as well

TABLE 25-I. PREPARATION\* AND COMPOSITION OF A DIALYZING SOLUTION AS USED IN A SKEGGS-LEONARDS ARTIFICIAL KIDNEY†

PREPARATION* AND COMPOSITION OF A DIALYZING SOLUTION AS USED IN A SKEGGS-LEONARDS ARTIFICIAL KIDNEY <sup>§</sup>										
CONSTITUENT	grams of salt in 4 liters of stock sol.	CONCENTRATIONS IN FINAL DILUTED DIALYZING SOLUTION							mgm%	
		Cl <sup>-</sup>	HCO <sub>3</sub> <sup>-</sup>	C <sub>3</sub> H <sub>5</sub> O <sub>3</sub> <sup>-</sup>	Na <sup>+</sup>	K <sup>+</sup>	Ca <sup>++</sup>	Mg <sup>++</sup>		Dextrose
		Milliequivalents per liter								
Stock solution A:										
NaCl	852.0	91.2			91.2					
KCl	45.0	3.8				3.8				
CaCl <sub>2</sub> ·2H <sub>2</sub> O	38.8	3.3					3.3			
MgCl <sub>2</sub> ·6H <sub>2</sub> O	24.4	1.5						1.5		
Lactic acid	170 ml.			12.1						
HCl	140 ml.	10.6								
Dextrose	200.0								125	
Stock solution B:										
NaHCO <sub>3</sub>	443.5		33.0		33.0					
NaOH	121.6				19.0					
Total (diluted):		110.4	33.0	12.1	143.2	3.8	3.3	1.5	125	

\* 450 ml. of each stock solution is made up separately; when ready to use the 2 stock solutions are added to 17,000 ml. tap water, making a total of 18 liters, (1/40 dilution). pH of the combined solution is tested and adjusted to 7.4 by adding a small amount of HCl or NaOH.

§ Procedure according to Bluemler et al ( 5i ).



Patient: V.N., 48 ♀ W, Transfusion reaction —  
acute renal failure

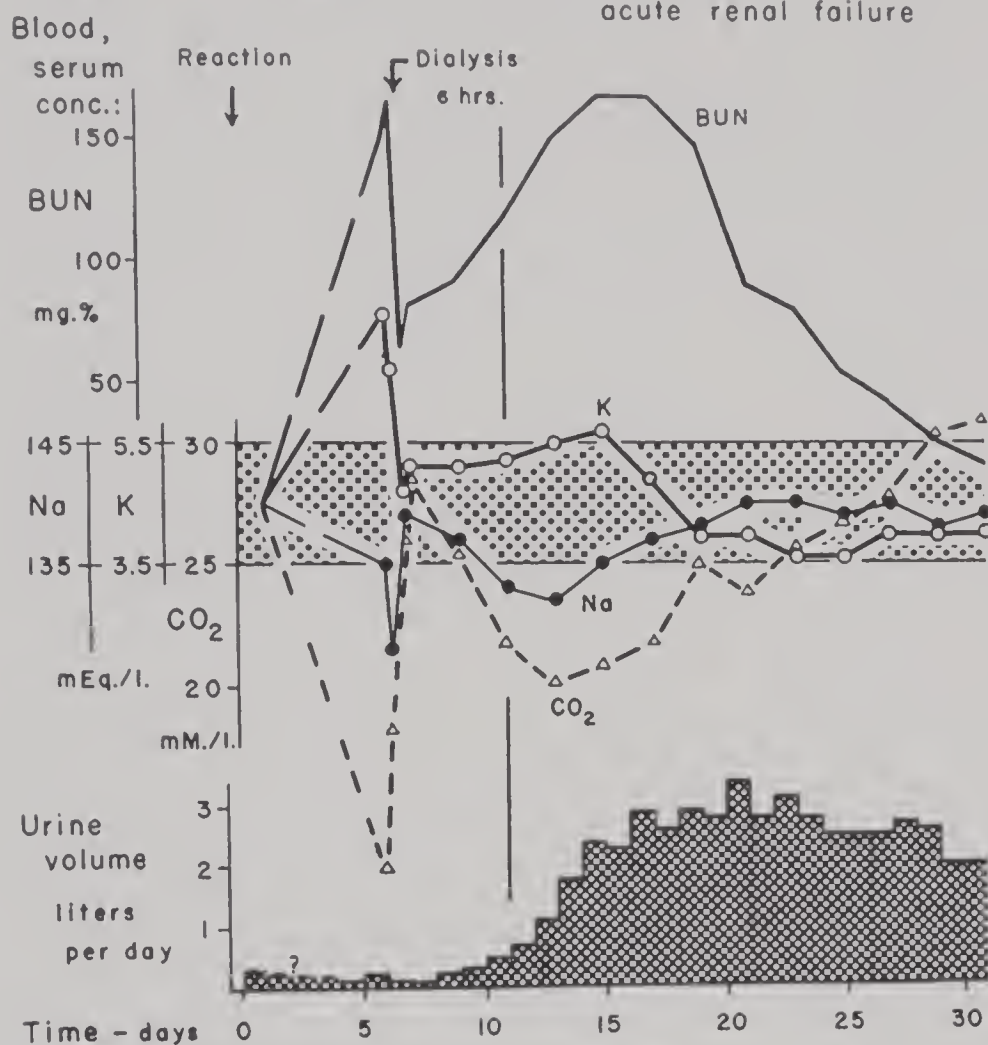


FIG. 25-5. EFFECT OF A SINGLE DIALYSIS WITH THE SKEGGS-LEONARDS ARTIFICIAL KIDNEY ON THE CONCENTRATION OF BLOOD UREA-NITROGEN IN A PATIENT WITH ACUTE RENAL FAILURE  
From Bluemle *et al.* (5i)

as diffusible solute, through a semipermeable membrane by the apposition of hydrostatic pressure to osmotic pressure of the restrained solutes (see figure 1-9). In the situation under discussion the term ultrafiltration refers to the movement from blood to dialyzing solution of water as well as certain solutes down a gradient of hydrostatic pressure. In the Skeggs-Leonards or Westinghouse-Alwall apparatus the hydrostatic pressures of the blood and dialyzing solutions can be readily controlled. We have found that the consequent shifts of water can easily be quantitated by serial weighings of the patient who is dialyzed on a stretcher-scale. While some workers have had indifferent success with this process in removing edema fluid, Miller and Leonards and ourselves have found ultrafiltration by the Skeggs-Leonards machine to be an effective and useful therapeutic process in some circumstances, in keeping with the findings in experimental animals (7b, 11a-c).

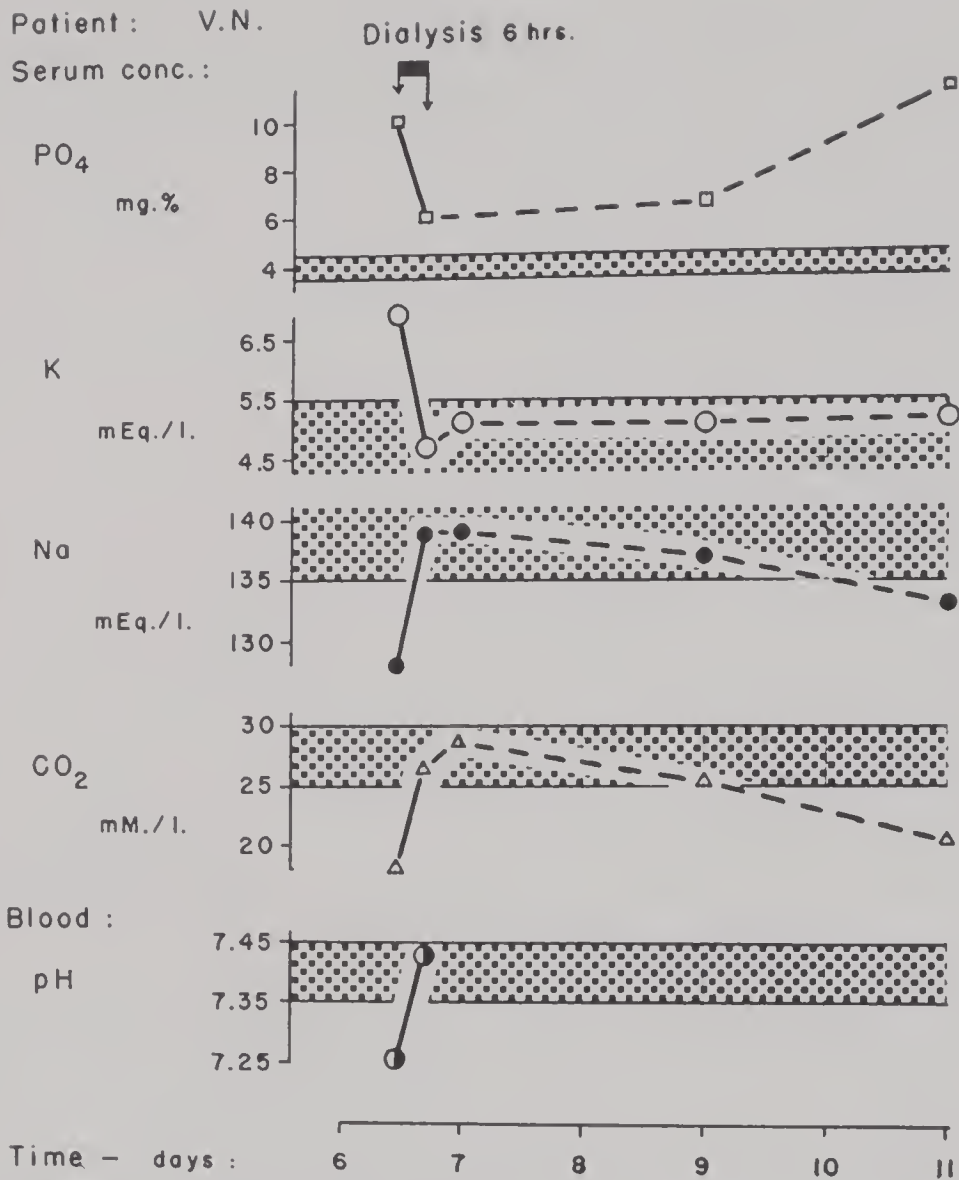


FIG. 25-6. EFFECT OF A SINGLE DIALYSIS WITH THE SKEGGS-LEONARDS ARTIFICIAL KIDNEY ON SERUM ELECTROLYTE CONCENTRATION AND BLOOD ACID:BASE INDICES, IN THE SAME PATIENT WITH ACUTE RENAL FAILURE SHOWN IN THE PRECEDING FIGURE  
From Bluemle *et al.* (5i)

This is illustrated in figure 25-7 in which 1500 milliliters of fluid were removed in this way from an overhydrated patient in acute renal failure, with concomitant clearing of the clinical signs of pulmonary edema. Miller and Leonards have removed six liters of fluid from such a patient during one run on their artificial kidney (11d). However, much needs to be learned of the hemodynamic factors which must condition this maneuver.

Clinical experience to date has been sufficiently extensive to establish the use of the artificial kidney as a safe procedure in the hands of experienced operators and to clarify many of the physiological and biochemical effects of the procedure. Kolff has treated many patients (12a), Merrill and

T.S.

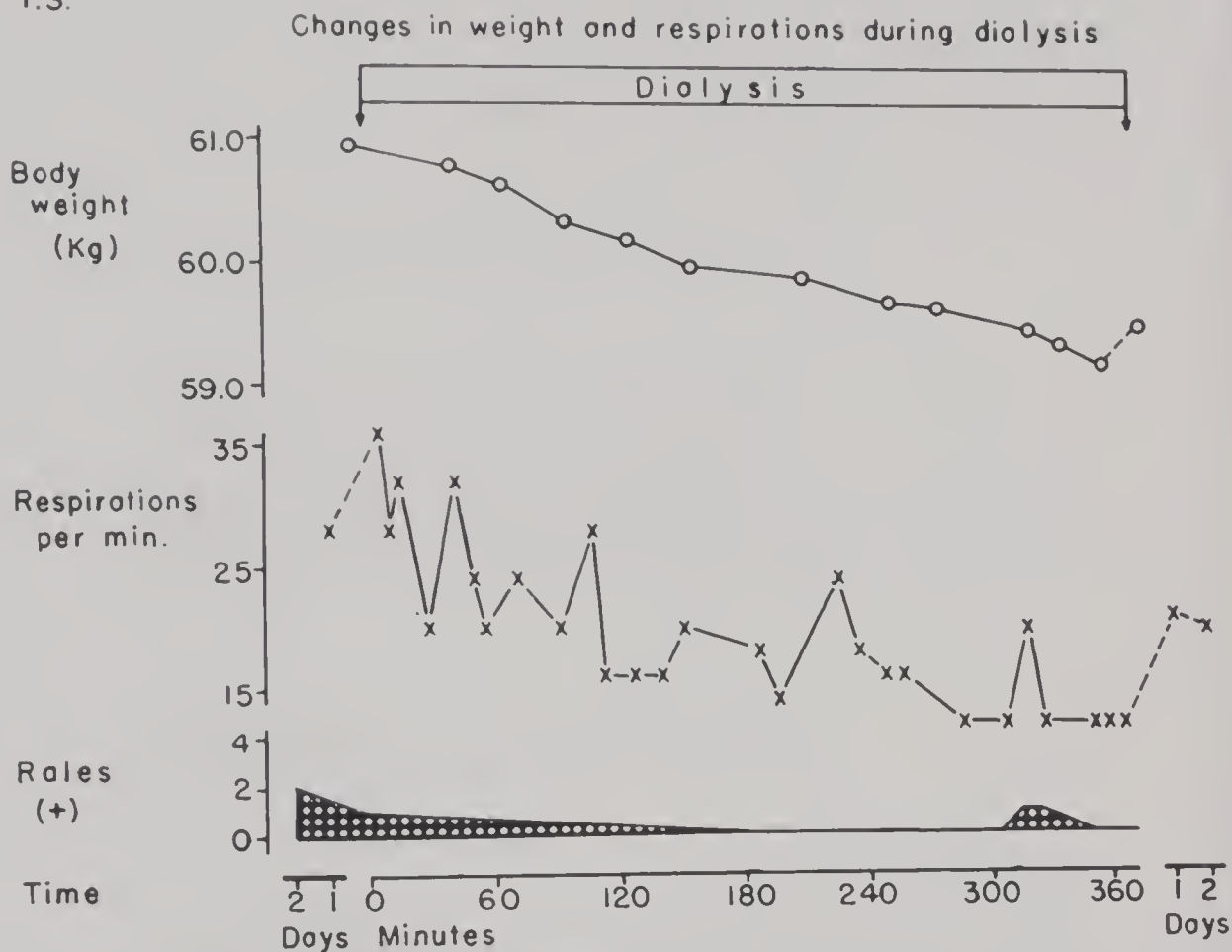


FIG. 25-7. USE OF THE SKEGGS-LEONARDS ARTIFICIAL KIDNEY AS AN ULTRAFILTRATOR TO REMOVE EDEMA FLUID, IN A PATIENT WITH ACUTE RENAL FAILURE

The application of a negative hydrostatic pressure led to a net loss from blood into the dialyzing solution of approximately 1500 ml. of fluid, as well as of retained solutes. This transfer of water from the patient is reflected in the drop in body weight. Concomitantly the pulmonary rales diminished and the respiratory rate returned toward normal. (From Bluemle *et al.* (5i).)

associates in Boston have probably had the widest experience in the world having performed over 400 clinical dialyses at the time of this writing (12b). The United States Army team in Korea attained rapidly an extensive military experience with the artificial kidney (4m, 12c), and many other workers too numerous to include in anything other than an inclusive review, have successfully used one or others of the main prototypes described above in civilian practice.

#### *E. Indications for Use*

Attitudes of responsible clinicians towards the artificial kidney range from the belief that there is no indication for it to the expectation of far too much from it. By some of the former it has been stated that in acute renal failure, as in acute tubular damage or "lower nephron nephrosis," the 20 to 30 per



cent mortality rate of good conservative therapy is no higher than that reported for those treated with an artificial kidney, and that therefore there is no indication for vivodialysis in this condition (2m). On the other hand some groups of workers, including the authors, believe that even with good conservative medical therapy the over-all mortality of this condition is closer to 50 per cent (13a, b). This higher mortality results from the inclusion in the series of many complicated cases with profound circulatory disturbances and high catabolic rates, as found in severe trauma (crush injuries, military wounds), in severe infection (septic abortion, liver abscesses), or following upon extensive operative procedures (pulmonary and cardiac surgery). In the opinion of the authors dialysis may be a lifesaving procedure in such a situation, though it is impossible to prove this statistically at this time. It is our impression that in these and in related situations the artificial kidney is a valuable *adjunct* to good conservative medical therapy, and does not represent a radical form of treatment.

It should be emphasized that dialysis has no place as a last-ditch measure to try to snatch from the jaws of death the patient who is moribund with irreversible changes. To determine when such a state impends requires careful judgment. We believe that dialysis should be instituted early in the course of anuria according to the clinical state of the patient and the "catabolic index" (12b), and be repeated if necessary later on. As a "rule of thumb" we usually urge dialysis on the fifth or sixth day of virtual anuria. The extraordinary clinical improvement in terms of clearing of sensorium, disappearance of nausea and return of appetite, which frequently occurs after dialysis, has impressed many of those who have used the artificial kidney. We do admit however that statistical analysis of a much wider experience is needed to prove beyond peradventure of a doubt that dialysis adds something over and above good medical management. To those who believe that such is the case, the following indications pertain.

**1. Acute renal failure** due to tubular necrosis (e.g., hemolytic reaction, nephrotoxins, shock with anoxia) is the chief clinical category in which dialysis should be considered. The indications in this situation are a) rapid clinical deterioration, b) a rapid catabolic rate or "index" as indicated by the rate of rise of BUN, plasma, creatinine, phosphate, and undetermined anion concentrations, and fall in total carbon dioxide content, c) increasing hyperkalemia with electrocardiographic evidence of cardiotoxicity which is unresponsive to other measures such as resin enemas, d) intractable pulmonary edema, or e) the continuation of virtual anuria for five or six days.

The dialyzer should not in general be used in acute glomerulonephritis since the prognosis of this disease is excellent. However, if far-advanced renal failure supervenes with the changes described in the preceding paragraph it should be applied without hesitation (14a).

**2. In chronic renal insufficiency** the indications for dialysis are certainly less urgent and have yet to be worked out. It is possible that life in such patients may be prolonged by repeated dialysis.

**3. Acute intoxication** by salicylates, bromides, or barbiturates has been shown to be successfully treated by dialysis (14b-g). The use of the artificial kidney in such situations is presumably indicated only where the severity of the poisoning suggests that the usual conservative methods of treatment may fail.

**4. Intractable edema** in congestive heart failure has been treated by ultrafiltration in an artificial kidney with varying success (7b). The indications for its use in this condition have yet to be established.

#### *F. Contraindications to Vivodialysis*

Aside from inexperience and inadequate apparatus, extracorporeal dialysis is primarily contraindicated by any bleeding tendency in the patient. This is especially true of those with gastrointestinal bleeding or intracranial hemorrhage. As indicated earlier, anticoagulation with heparin has to be attained to a greater or lesser degree in order to shunt the blood from the patient. Promotion of hemorrhage by this measure, therefore, may threaten the patient's life.

### **IV. Replacement of Blood as an Alternative to Vivodialysis**

The removal and replacement of blood is not of course a dialytic procedure but it is discussed at this point because it has been employed as an alternative to gastrointestinal lavage, peritoneal irrigation, or extracorporeal vivodialysis.

#### *A. Exchange Transfusion*

Exsanguino-transfusion consists of repeatedly withdrawing blood from the patient and replacing it with equal volumes of citrated normal blood. Seven or eight liters may be exchanged over some six hours which may replace up to 80 per cent of an adult patient's blood volume. Successful treatment of acute renal failure by this method has been reported (3f, 15a). It is perhaps best known as a neonatal means of saving the life of erythroblastotic infants by replacing Rh positive red cells with Rh negative red cells and so halting intravascular hemolysis. In the severely uremic patient this method is more widely available, though less efficient than dialysis, in removing the retention products outlined in the previous section.

#### *B. Cross Transfusion*

This procedure has been attempted in the treatment of renal failure by connecting the circulation of the patients with that of a donor subject with

normal kidneys (15b). The purpose is to permit the latter to clear the blood of the former. This is hazardous to the donor because of possible incompatibility of blood types and consequent hemolytic reaction and can prove fatal. With the availability of modern methods of dialysis this procedure should never be used.

**SUMMARY:** Living membranes such as those of the peritoneum and gastrointestinal tract, or artificial ones such as cellophane, can be used to permit bidirectional exchanges of water and solutes between the body fluids and external baths. The concentrations of constituents of the bath determine the direction of transfers. Thus, a lower level potassium in the bath permits withdrawal of this electrolyte from the body. The relative inefficacy or complexity of gastrointestinal perfusion procedures and the problems of infection, blockage, protein loss and acid-base regulation in peritoneal lavage have led to the development of several types of artificial kidneys for dialysis. Those which provide a rigid support of the cellophane also may remove water by ultrafiltration. Devices of this type have proved useful in acute renal failure, particularly in therapy of hyperkalemia and in intoxications with salicylates and barbiturates. They also may prove to have a role in producing partial remissions in chronic renal diseases with superimposed acute exacerbations or complications.

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## *Appendix*

### THE BALANCE TECHNIC

The balance technic for determining exchanges of any body constituent consists of an algebraic summation of all intake and output as determined by direct measurements or by means of estimates within experimentally established parameters. The actual amounts involved are often expressed per unit of body mass so that the magnitude of the change can be related percentage-wise to the endogenous stores of the particular component under scrutiny. It is also customary to subdivide the net or external balance into "extracellular" and "cellular" components.

#### **I. Balance Procedure**

The following outline presents a sample of one of several procedures which can be used in conducting balance studies. The sequence is important; experience indicates that even after many studies a check list is still indispensable if blunders and omissions are to be avoided.

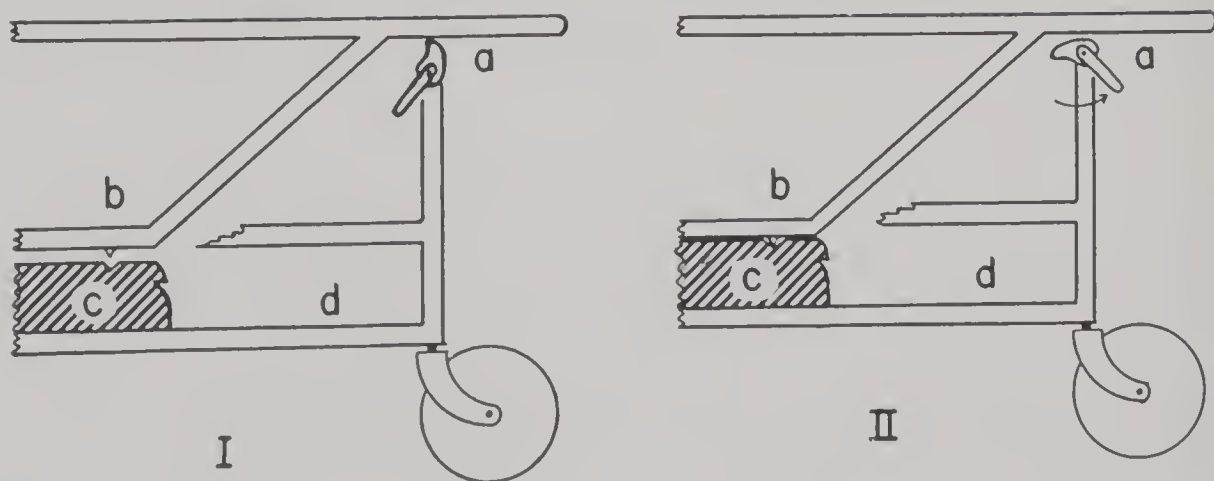
In the postabruptive state, and, if possible, after several days trial maintenance on the dietary regimen to be used during the study:

1. Empty bladder completely.
2. Obtain accurate body weight without clothing (see fig. A-1).
3. Withdraw blood for serum and analyses.
4. Start balance period (7:00 a.m.).
5. Administer carmine red capsule (0.3–0.6 gram) as stool marker.
6. Accurate intake of water, duplicate diet or fortified milk formula at intervals as desired but ending each day at midnight.
7. Collect all stools after discarding specimens marked by initial dose of dye; avoid contamination with urine if experiment demands this.
8. Collect all urine with preservative as indicated.
9. Collect vomitus, drainage, etc.
10. Note any intervals of sweating.





A



B

FIG. App.-1

A. The Stretcher-scale.

B. Diagram of the principle of suspension. In I, the stretcher top is supported by the cam (a) so that the truss (b) is out of contact with the scale platform (c) which is mounted on the undercarriage (d). In II, a turn of the handle and cam (a) has permitted the truss (b) and hence the stretcher top, to be supported entirely by the scale platform (c) so that weighing may be made.

This scale was designed by, and described by, L. W. Bluemle, Jr. and J. R. Elkinton (2).

11. End balance period as in 1, 2, and 3 but save urine.
12. Administer carmine red and continue stool collection through and including the marked stools.

## II. External or Net Balances

In external balances all input via oral and parenteral routes and all removal or loss in blood, urine and feces, as well as the output through the lungs, skin and any other route are taken into account.

### A. *Measurements and Estimates of Solids and of Water*

In the usual analysis of duplicate diets to determine intake, particular care must be given to exact matching of consumed items and to thorough mixing so that representative aliquots are obtained for chemical determination. Incineration or wet ashing is a prerequisite for the latter. The expense and labor involved in this aspect of balance studies can be materially decreased however by use of whole milk or dialyzed milk formulae of known composition. These can be fortified with milk protein and carbohydrate to provide sufficient calories and nitrogen and can be supplemented with iron and vitamins. This type of maintenance diet minimizes the need for repeated diet analyses, allows an accurate measurement of all wasted intake, lends itself readily to the preparation of low sodium or low potassium regimens, is an excellent vehicle for supplementary solutes, and finally permits an estimate of the probable electrolyte and nitrogen content of formed stools without actual analyses of feces (table A-I). Among the disadvantages one should cite the fact that some adults do not find these formulae as palatable as do children and that their lack of bulk and the high calcium content may be undesirable in certain experiments. Some of these objections can often be met by supplements of known composition such as rice, fruits, etc. This is especially effective in enhancing the palatability of the intake in studies extended over intervals of days or weeks.

The water in general diets has to be obtained by adding the obvious volumes which have been taken to the water content of the diet itself as determined by desiccation. In the case of milk formulae it should be remembered that the addition of solutes will alter the percentage of water in the final mixture. In both types of regimens the electrolyte composition of tap water must be kept in mind when intake of any element is being rigidly controlled.

### B. *Measurements and Estimates of Output*

**1. In urine.** From the quantitative viewpoint the loss in urine is usually the most significant component in the output column. Calcium, iron and other elements or compounds which are ordinarily eliminated in propor-

A

mEq.

Daily intake, output, and balance of sodium

B

C

D

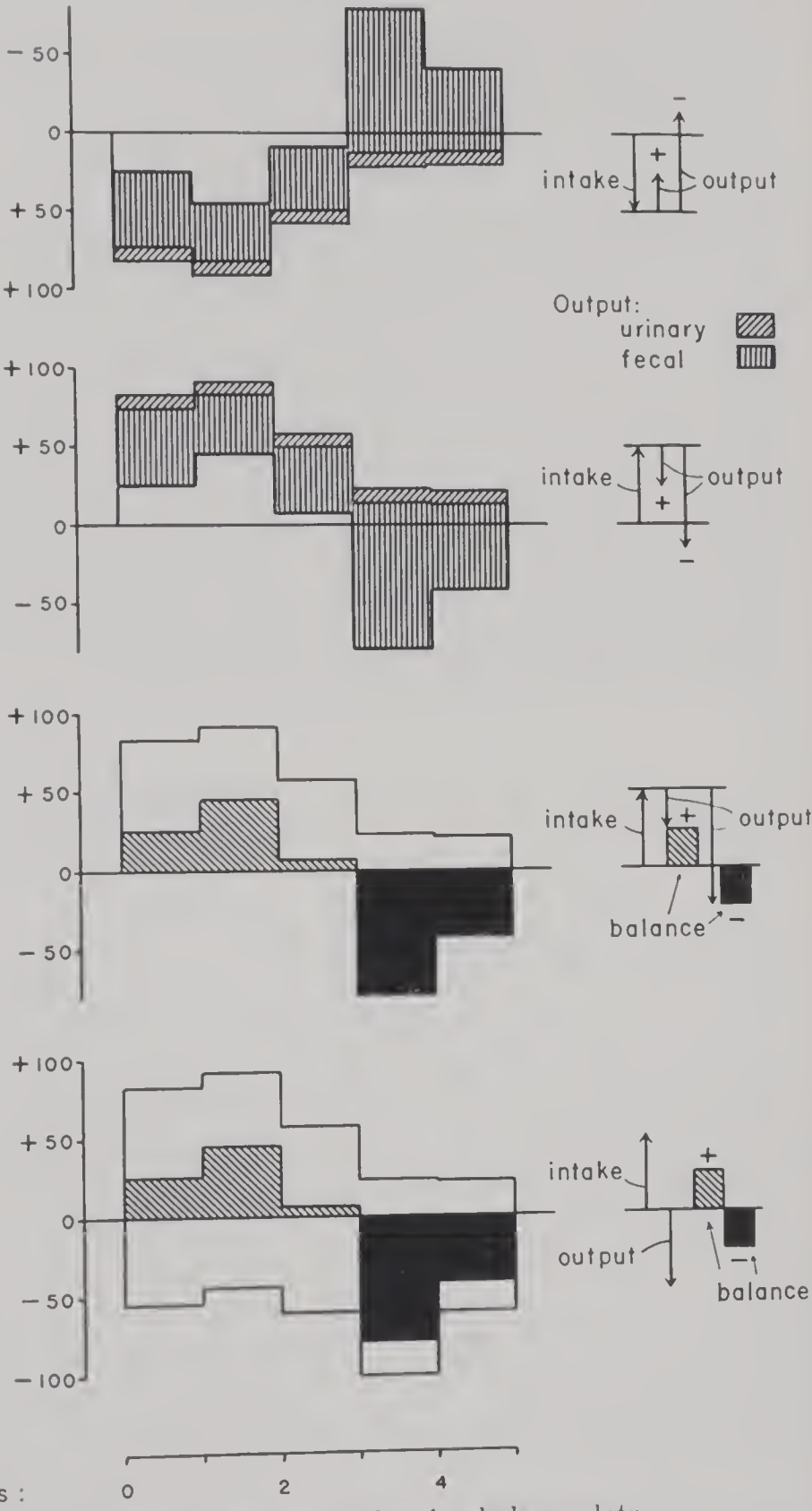


FIG. App.-2. Different methods of charting balance data.

The daily intake, output, and balance of sodium are plotted in four different ways. These data are taken from an edematous patient receiving cation exchange resin and varying amounts of dietary sodium (case presented in greater detail in Fig. 13-5).

A is the classical method of Albright *et al.* (3a) in which intake is plotted downward



tionately greater amounts in feces than in urine represent obvious exceptions to this generalization. Also disease states characterized by diarrhea, vomiting and intestinal drainage or by sweating, exudation or transudation, can increase the magnitude of the losses via the gastrointestinal tract and skin to the point where they exceed the excretion in urine. This is especially apt to be true of constituents such as sodium and chloride which may virtually disappear from the urine with, for example, depletion of body stores. Furthermore, oliguria or anuria may minimize the renal contribution so that output via other routes becomes the important determinant of the nature and the amount of the losses from the body even though these may not be increased above levels characteristic in health.

**2. In feces.** Under the experimental conditions employed in studies in which almost all of the excretion of a component occurs via some route other than the intestinal tract, the output in formed stools can usually be neglected. Liquid diarrheal stools on the other hand should always be analyzed because of the unpredictable and frequently high content of electrolytes.

Collection of the feces in a wide mouth tared glass container and especially in one which can be attached directly to a blending machine, greatly simplifies the processing of the specimen for analyses. It is obvious that if output is to be partitioned between urine and stools that admixture of the two must be avoided during collection. Storage of the stool overnight or longer in distilled water together with several milliliters of concentrated sulfuric acid facilitates the measurement of representative aliquots for analysis. This should be done immediately after adding sufficient distilled water, mixing and determining the final volume of the suspension. Suffi-

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from the zero base-line and output upward from the intake. Urinary output is indicated by diagonal cross-hatching, fecal output by vertical lining. Negative balances are those portions of the columns above the zero line, and positive balances are represented by blank areas below the zero line; in this way losses from the body are emphasized.

*B* is the method used by the authors throughout this book and elsewhere (3b, e); it is the same as that of Albright *et al.* except that it is inverted so that positive balances are plotted upward and negative balances downward. Both of these methods have the advantage that the various types of output can be visualized; thus it is shown that the major loss of sodium is fecal rather than urinary.

*C* is the method used by Moore and Ball (3d). Total intake and total output are plotted as in *B*, but the balance is emphasized by the cross-hatched areas above, and the solid areas below, the zero line. The different routes of excretion are not shown and in this case, therefore, the information is not conveyed that the major sodium loss was in the feces.

*D* differs from *C* in that the output is plotted downward from the zero base-line rather than from the intake. The balance is superimposed as an independent plot and is emphasized as in *C*. Likewise, the different routes of excretion are not shown.

cient accuracy can usually be obtained by using 10 or 20 cc serological pipettes with wide delivery openings. Analyses for sodium and for potassium by means of flame photometry are readily possible if the aliquots are wet ashed by the Wallace technic (la). The measurement of stool chloride by the Hald method can be further simplified by mass rather than individual digestion of the samples (lb). Stool nitrogen is determined by the Kjeldahl procedure after pipetting of the samples directly into the digestion flask. The experience in this laboratory concerning analyses for other stool components is insufficient to permit authoritative comment.

In balance experiments in which the subject is maintained on either a whole milk or low sodium milk formula the fecal excretion of sodium, chloride, potassium and nitrogen can be estimated from the means and standard deviations which the authors have accumulated in control studies (lc). The findings, Table A-I, have been expressed per 100 grams of formed stool per day, and save in the case of nitrogen, per gram of nitrogen.

**3. Output through skin, via lungs, in sweat, transudates and exudates.** In the nonsweating healthy subject evaporation of water through the skin and respiratory tract is second in volume only to water losses in urine. If the renal output is impaired or decreases in adjustment to inadequate intake, then the insensible perspiration becomes the preponderant and in large measure, irreducible route of body water loss. In the adults with ordinary levels of metabolic activity this amounts to about one liter each 24 hours. In actual practice its magnitude is taken to be the unexplained difference between the algebraic sum of the intake and output of water. This figure will of necessity reflect the inherent and unrecognized errors in measurements of weight and volume, and as such must represent only an approximate estimate. Similar errors are present in utilizing the metabolic mixture or the caloric expenditure as an index of insensible water loss (ld). If more accurate data are needed, then measurements of body weight change by means of a sensitive scale or balance are necessary.

The extrarenal water losses become greater with sweating, vomiting, draining fistulae, exuding surfaces, and with diarrhea. Actual weight measurements of such water losses are feasible though often laborious. In general this aspect of balance studies is most readily simplified by studious avoidance of situations in which quantification is either difficult or impossible.

Quantitatively significant losses of electrolytes can and do occur through the intact nonsweating skin (le). In balance studies conducted in infants these are of sufficient magnitude to warrant careful collection and analyses of bath water (lf), but this tedium is usually avoided, with as yet unestablished justification, in adult subjects. Incidentally, no data are available as to whether exhalations of the lungs or integument contain any significant

amounts of elements ordinarily considered to leave the body in nonvolatile form.

When sweating, exudation and transudation are superimposed upon the insensible perspiration, the balance study necessitates quantitative measurements of these or it must be abandoned. In the former, careful collections on properly processed clothing or other material have been employed.

### III. Calculations of the External Balance and of the Extracellular and Cellular Components

The authors have found it helpful to utilize printed forms in setting up balances. Tables A-II through A-VI shows work sheets employed during the balance procedures. Forms used for calculations are presented as tables A-VII through A-X. In the first of these, summarized information pertinent to the calculations of the external balance is recorded. Serum and blood values are entered in the next table and corrections for serum water and the Donnan effect are made, in this instance, for chloride, sodium and potassium. In the following table the chloride space is used to estimate changes in the so-called extracellular water, sodium and potassium. In table A-X the important correction for changes in nonprotein nitrogen is introduced into the net or external balance of nitrogen and the "cell balance" of potassium is related to protein changes. The formulae have been taken from our publications, and are identical in substance with previous descriptions from this and other laboratories as illustrated in chapter 3 of this text. Tables A-XI through A-XIII illustrate forms useful for final presentation of data (see chap. 3 for exact equations).

### IV. Interpretations

The interpretation of values obtained by balance studies presents many insufficiently appreciated problems. Part of the explanation for the latter undoubtedly lies in the fact that the completion of the balance procedure, despite the simplicity of its concept, requires the gathering of a formidable array of data. The latter naturally limits the number of studies which can be conducted and at the same time results in a tendency to generalization from a small group of observations. The problem is further complicated, as will be seen, by the introduction of certain reasonable assumptions the errors in which will inevitably be compounded by nature of the algebraic summation. In the discussions which follow emphasis will be placed upon identification of original and derived data and indicating the currently justifiable deductions.

#### A. *Net or External Balances*

Four pertinent comments should be made concerning external balances. These deal with the effects of antecedent diet and intake, the length of



the study, the assignment of fecal excretion data, and finally, anabolism and storage as factors in the output.

1. It is obvious that an unrestricted regimen may provide the organism with excesses of certain constituents. These will be eliminated in subsequent intervals and could be erroneously ascribed to some other variable in the balance study. This blunder can be avoided by prebalance periods during which the subject is maintained on the same regimen which will be employed in the study itself. Frequent subdivisions of the balance study into shorter intervals will also serve to detect the effects of antecedent intake but greatly increases the laboratory work and obviously introduces the possibility of cumulative errors. On the other hand, in depleted subjects this cannot be done, if repletion is to be demonstrated.

2. Insofar as duration of the balance study is concerned it is the general custom to extend it over several days. Five to seven days have proved sufficient in our hands in establishing control values for the subsequent introduction of variables which influence sodium, potassium, chloride and nitrogen exchanges. This range has also proved adequate for calcium studies. Longer periods may be necessary in the case of elements or compounds with a greater biological half-life, and intervals as short as a few hours may have to be used with rapidly eliminated constituents.

3. Ordinarily the fecal excretion of any item under study is assigned to the balance period demarcated in time by carmine red administration. It should be pointed out that in actuality the gastrointestinal contents present at the time of the study differ greatly in composition from those of the formed stool which is subsequently obtained for analysis. In the interim constituents have been removed and added in unmeasured quantities. In actual practice this dilemma is ignored by assuming that the contents of the intestinal tract are part of the body stores. Since there is no obvious resolution evident, experiments should be designed to minimize the quantitative importance of the intestinal and fecal components in the over-all balance.

4. It should be constantly remembered that a host of processes influence retention or excretion from the body. Thus one might logically expect that destruction of tumor tissue by means of nitrogen mustard should release potassium and nitrogen for excretion in the urine. However these elements will not be lost from the body if they are incorporated into other cells (1h). Moreover retention *per se* cannot be taken as a conclusive indication of the prior existence of deficits of a particular constituents. The lag in the excretion of cations administered in excess of daily needs is a well-known example of the temporary sojourn which might be interpreted as repletion.

### B. Extracellular and Cellular Balances

Differences of opinion are extant concerning the validity of changes in the chloride space as an index of extracellular volume. For purposes of this discussion it is probably sufficient to point out that the test substance which gives the smallest volume of distribution is not *a priori* the most precise index of the extracellular space. Evidence is available for example that inulin penetrates much more slowly into connective tissues which are, from the viewpoint of their composition, more closely related to extracellular than to cellular fluid. Rather than assume a premature position on this subject the writers prefer to emphasize three sets of fundamental facts concerning the so-called extracellular-cellular partitions.

1. Electrolytes can enter and leave cells in response to a wide variety of processes such as overfeeding, depletion, dehydration, muscular activity, glycogen deposition, tissue formation, interruption of carbohydrate metabolism, anoxia, etc. At this point of our knowledge establishment of the fact is more important than quantification.

2. Whether or not the concentration of a particular component in cell water is altered will depend upon whether or not comparable changes occur in cell water itself. In the latter changes in the osmotic activity of cell base may play a heavy role.

3. The changes in the total amounts and concentrations of electrolytes and of water involved in any net transfer need not be uniformly distributed throughout the "non-extracellular" space, irrespective of the index employed.

All three of these facts are compatible with the hypothesis that external balances of any component can represent changes in cells, with or without alterations demonstrable by means of tissue analysis, and with or without increases or decreases in the osmotic activity of cell solutes.

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TABLE APP.-I

COMPOSITION OF FECES DURING MAINTENANCE ON MILK FORMULAE										
DIET	Na		K		N		Cl		N	
	mEq./d.	mEq./100 g.	mEq./d.	mEq./100 g.	mEq./1. g.	mEq./d.	mEq./100 g.	mEq./1. g.	mEq./d.	mEq./100 g.
SODIUM-FREE MILK*	Mean	2.3	2.3	8.1	12.3	12.2	.7	.8	.9	.9
	No.	44	48	47	48	46	46	44	48	46
	S.D.	1.1	2.1	5.3	8.2	7.7	.7	.5	.4	.3
-----										
WHOLE MILK**	Mean	1.9	2.3	12.2	14.6	14.6	1.3	1.2	1.4	1
	No.	38	38	40	38	34	38	37	36	38
	S.D.	1.4	1.6	6.8	7	5	1.3	.7	1	.4

\* Composition of low-sodium milk formula: Na = 1.1 mEq./l; K = 44.9 mEq./l; Cl = 18.5 mEq./l; N = 5.3 g./l.  
\*\* Composition of whole milk formula: Na = 26 mEq./l; K = 37 mEq./l; Cl = 31 mEq./l; N = 5.4 g./l.

TABLE APP.-II

HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA  
NUTRITION HISTORY

Last name	First Name	History Number			
Location	Service	Date	Sex	Age	Marital Status
Previous Diet		Hgt.	Act.wgt.	Desired Weight	

INTAKE:	FOOD	TOTAL PER DAY or week
---------	------	--------------------------

	MILK-WHOLE	
	SKIM	
	CANNED	
Morning:	CHEESE	
	EGGS	
	MEAT	
	FISH	
	LEGUMES	
	BACON	
	CREAM	
	BUTTER	
Noon:	OTHER FAT	
	FRUIT-RAW	
	COOKED	
	VEGETABLES-RAW	
	COOKED	
	POTATOES	
	POTATO SUBSTITUTE	
Night:	CEREAL-REFINED	
	WHOLE GRAIN	
	CRACKERS	
	SUGAR	
	DESSERTS	
	TEA	
	COFFEE	
Between Meals:	ALCOHOL	
	WATER	
	VITAMINS	
	SALT	
	OTHER SEASONINGS	
	TOTAL FLUID INTAKE	
	MISCELLANEOUS	

FOOD DISLIKES AND IDIOSYNCRASIES

COOKING FACILITIES

ADEQUACY OF INCOME

SUMMARY AND RECOMMENDATIONS

TABLE APP.-III

NURSES' INTAKE - OUTPUT RECORD

PARENTERAL FLUIDS			ORAL FLUIDS			OUTPUT					
Type of fluid	Time	Amt. Start.	Time	Amt. Absorb.	Type	Time	Urine	Stool	Vomit	Blood	Other

TABLE APP.-IV

DAILY DIET RECORD

Name	Diet Number		Date		Type Diet	
MEAL PLAN	Check When Weighed	Check When Served	Fluid	Weight	FOOD	Returns
						NET INTAKE

TABLE APP.-V

INTAKE CALCULATION SHEET

PATIENT \_\_\_\_\_ ROOM \_\_\_\_\_ DATES: from 7 a.m. \_\_\_\_\_ to 7 a.m. \_\_\_\_\_

FOOD CONSUMED      gms.      cc.      P      F      CHO      Cal      Na.      K      Cl      N      Ca      P      Mg.      A      Solids



TABLE APP.-VI

Chemical Section of the Department of Medicine and Metabolic Unit,  
Hospital of the University of Pennsylvania

FLUID THERAPY CONTROL CHART

PATIENT

24 Hr period ending:		7 a.m.					7 a.m.					7 a.m.						
Constituents (H <sub>2</sub> O ⇌ vol)		H <sub>2</sub> O	Cl	Na	K	N	H <sub>2</sub> O	Cl	Na	K	N	H <sub>2</sub> O	Cl	Na	K	N		
		cc	meq	meq	meq	gm	cc	meq	meq	meq	gm	cc	meq	meq	meq	gm		
I N T A K E	ENTERAL          PARENTERAL	H <sub>2</sub> O																
TOTAL		H <sub>2</sub> O, Cl, Na, K, N																
		P	C	F	Cal.		P	C	F	Cal.		P	C	F	Cal.			
O U T P U T	Urine																	
	Vomit + Wangenst																	
	Drainage (net)																	
	Feces																	
	Blood																	
	Insensible (estim)																	
	Total																	
BALANCE (+ or -)																		
Chemical and clinical observations and estimated body fluids, (at end of above period)																		
Weight		Δ Wt.		kg		kg		kg		kg		kg		kg		kg		
B L O O D	B <sup>+</sup> UN (8-18)	pH (7.36-7.46)	UN	mg%	pH	UN	mg%	pH	UN	mg%	pH	UN	mg%	pH	UN	mg%	pH	
	NPN (22-35)	CO <sub>2</sub> (20-24)	NPN	mg%	CO <sub>2</sub>	mmH	NPN	mg%	CO <sub>2</sub>	mmH	NPN	mg%	CO <sub>2</sub>	mmH	NPN	mg%	CO <sub>2</sub>	
	Hb (12.7-16.9)	pCO <sub>2</sub> (35-48)	Hb	gm%	pCO <sub>2</sub>	mmHg	Hb	gm%	pCO <sub>2</sub>	mmHg	Hb	gm%	pCO <sub>2</sub>	mmHg	Hb	gm%	pCO <sub>2</sub>	
	Hkt (41-47)	BB (48-53)	Hkt	%cells	BB	meq/l	Hkt	%cells	BB	meq/l	Hkt	%cells	BB	meq/l	Hkt	%cells	BB	
S E R U M	Na (134-144)	CO <sub>2</sub> (23-31)	Na	meq/l	CO <sub>2</sub>	meq/l	Na	meq/l	CO <sub>2</sub>	meq/l	Na	meq/l	CO <sub>2</sub>	meq/l	Na	meq/l	CO <sub>2</sub>	
	K (3.5-5.3)	Cl (99-107)	K	"	Cl	"	K	"	Cl	"	K	"	Cl	"	K	"	Cl	
	Cr. (0.3-1.3)	Δ <sup>+</sup> (0-11)	Cr.	mg%	Δ	"	Cr.	mg%	Δ	"	Cr.	mg%	Δ	"	Cr.	mg%	Δ	
	Ca (9.6-11.6)	PO <sub>4</sub> (3.3-4.2)	Ca	mg%	PO <sub>4</sub>	mg%	Ca	mg%	PO <sub>4</sub>	mg%	Ca	mg%	PO <sub>4</sub>	mg%	Ca	mg%	PO <sub>4</sub>	
	Total Prot	Alb	Glab	TP	gm%		TP	gm%			TP	gm%			TP	gm%		
B O D Y	TOTAL H <sub>2</sub> O (W) (I)	Δ W	W	I	Δ W	I	W	I	Δ W	I	W	I	Δ W	I	W	I	Δ W	
	Ex <sup>+</sup> cell H <sub>2</sub> O (E) (")	Δ E	E	"	Δ E	"	E	"	Δ E	"	E	"	Δ E	"	E	"	Δ E	
	In <sup>+</sup> cell H <sub>2</sub> O (I) (")	Δ I	I	"	Δ I	"	I	"	Δ I	"	I	"	Δ I	"	I	"	Δ I	
	ClE (meq)	Δ ClE	ClE	meq	Δ ClE	meq	ClE	meq	Δ ClE	meq	ClE	meq	Δ ClE	meq	ClE	meq	Δ ClE	
	NaE (")	Δ NaE	NaE	"	Δ NaE	"	NaE	"	Δ NaE	"	NaE	"	Δ NaE	"	NaE	"	Δ NaE	
	KE (")	Δ KE	KE	"	Δ KE	"	KE	"	Δ KE	"	KE	"	Δ KE	"	KE	"	Δ KE	
	KI (")	Δ KI	KI	"	Δ KI	"	KI	"	Δ KI	"	KI	"	Δ KI	"	KI	"	Δ KI	
	NaI (")	Δ NaI	NaI	"	Δ NaI	"	NaI	"	Δ NaI	"	NaI	"	Δ NaI	"	NaI	"	Δ NaI	
	PI Vol (PV) (cc)	Δ PV	PV	cc	Δ PV	cc	PV	cc	Δ PV	cc	PV	cc	Δ PV	cc	PV	cc	Δ PV	
	BI Vol (BV) (")	Δ BV	BV	"	Δ BV	"	BV	"	Δ BV	"	BV	"	Δ BV	"	BV	"	Δ BV	
C V	Edema-Periph	Pulmon																
	Arterial p	Venaous p																
• Estim normal values in ( )		Remarks																
† See over																		

TABLE APP.-VII

INTAKE AND OUTPUT DATA: CALCULATION OF EXTERNAL BALANCES													
Subject	Age			Sex			Unit #			Diagnosis			

		INTAKE						OUTPUT						EXTERNAL BALANCE					
Period	Hrs	Vol cc	Cl mEq	Na mEq	K mEq	N g	CHO g	Vol cc	Cl mEq	Na mEq	K mEq	N g	CHO g	Vol cc	Cl mEq	Na mEq	K mEq	N g	CHO g

TABLE APP.-VIII

BLOOD AND SERUM SOLUTES; CONCENTRATIONS IN WATER, INCLUDING DONNAN FACTOR													
Subject	Age			Sex			Unit #			Diagnosis			

Period	Hrs	Sugar mg%	NPN mg%	HCO <sub>3</sub> mEq/l	Cl mEq/l	Na mEq/l	K mEq/l	H <sub>2</sub> O g/l	$\frac{[Cl_S]}{[w_S] \times 0.95} = [Cl_{ECW}]$	$\frac{[Na_S] \times 0.95}{[w_S]} = [Na_{ECW}]$	$\frac{[K_S] \times 0.95}{[w_S]} = [K_{ECW}]$

TABLE APP.-IX

CALCULATION OF CHANGES IN EXTRACELLULAR H <sub>2</sub> O, AND IN EXTRACELLULAR AND CELLULAR NA AND K						
Time Hrs.	Body Wgt. Kg.	$\frac{(ECW_1)[Cl_1]_{ECW} + bCl_1}{[Cl_2]_{ECW}}$	$\Delta ECW$ L	$\frac{(ECW_2)[Na_2]_{ECW} - (ECW_1)[Na_1]_{ECW}}{(ECW_2)[K_2]_{ECW} - (ECW_1)[K_1]_{ECW}}$	$\Delta K_{ECW}$	$\frac{(Na_{ICW})}{bNa - (\Delta Na)_{ECW}} = (\Delta K)_{ICW}$

TABLE APP.-X

CALCULATION OF BALANCES OF N AND K			
Subject _____ Age _____ Sex _____ Unit# _____ Diagnosis _____			
Period Hrs	Body Wgt. Kg.	$(Kg) \times 0.65 \times \frac{\Delta NPN \times 10}{1000} = bNPN$	$bN - bNPN = bN'$
			$(bN') (2.38) = bK_N$
			$\Delta K_{ICW} - bK_N = \Delta K'_{ICW}$



TABLE APP.-XI

BODY WEIGHT AND ANALYSES OF BLOOD AND SERUM

Subject	Time	Therapy	Body Wgt. (kg)	Sugar (mgm%)	NPN (mgm%)	HCO <sub>3</sub> (mEq/l)	Cl (mEq/l)	Na (mEq/l)	K (mEq/l)	Ca (mgm%)	P (mgm%)	H <sub>2</sub> O (g/l)	Protein (g%)
(Age-Sex)													

TABLE APP.-XII

INTAKE DATA AND URINE AND STOOL OUTPUT

Subject		Time		Therapy		Intake					Urine					Stool						
Age-Sex						Fluid	Cl	Na	K	N	Vol	Cl	Na	K	TN	NPN	Wgt	Cl	Na	K	N	
						(l)	(mEq)	(mEq)	(mEq)	(gm)	(l)	(mEq)	(mEq)	(mEq)	(gm)	(gm)	(gm)	(mEq)	(mEq)	(mEq)	(gm)	(mEq)

TABLE APP.-XIII

EXTERNAL, EXTRACELLULAR, AND CELL BALANCES

Subject	Time	Therapy	EXTERNAL BALANCE				EXTRACELLULAR BALANCE				CELL BALANCE			
			Cl (mEq)	Na (mEq)	K (mEq)	N (gm)	H <sub>2</sub> O (l)	Na (mEq)	K (mEq)	N (gm)	Na (mEq)	K (mEq)	N (gm)	

TABLE APP.-XIV

SAMPLE THIRTY MILLIGRAM SODIUM DIET (1490 calories)

			Prot. (gms)	Fat (gms)	CHO (gms)	Na (mgm)	K (mgm)
BREAKFAST							
ORANGE JUICE	50	grams	-	-	5	0.25	95
OATMEAL	50	grams	1	-	7.5	0.5	85
TOAST (UNSALTED)	12.5	grams	1	-	7.5	0.5	9
BUTTER (UNSALTED)	5	grams	-	5	-	0.25	0.2
SODIUM FREE MILK	140	grams	4	5	6	3.0	160
CASEC	10	grams	8.8	0.2	-	1.0	
Subtotal			14.8	10.2	26.0	5.50	349.2
DINNER							
POTATOES	100	grams	2	-	15	0.8	410
GREEN BEANS	50	grams	1	-	1.5	0.45	150
BREAD	25	grams	2	-	15.0	1.0	18
BUTTER	20	grams	-	20	-	1.0	0.8
SODIUM FREE MILK	240	grams	8	10	12.0	6.0	320
COCA-COLA	120	grams	-	-	11.4	1.2	62
TOMATO SALAD	50	grams	-	-	-	1.5	115
ORANGE	100	grams	-	-	10.0	0.3	170
CASEC	5	grams	4.4	0.1	-	1.0	-
Subtotal			17.4	30.1	64.9	13.25	1245.8
SUPPER							
BEAN SOUP	100	grams	1.23	-	5	0.3	433
MACARONI	150	grams	9.75	0.8	57	0.7	120
BREAD	25	grams	2.0	-	15	1.0	18
BUTTER	10	grams	-	10	-	0.5	0.4
SODIUM-FREE MILK	120	grams	4	5	6	3.0	160
COCA-COLA	60	grams	-	-	5.7	0.6	31
GREEN PEPPER	as desired		-	-	-	-	-
CUCUMBER	50	grams	-	-	-	0.5	115
PEARS (RAW)	50	grams	-	-	7.9	2.0	100
CASEC	10	grams	8.8	0.2	-	2.0	
Subtotal			25.78	16.0	96.6	10.6	977.4
TOTAL			58.00	56.0	187.5	29.5	2572
			milliequivalents			1.3	66

Supplemented with iron and vitamins

TABLE APP.-XV

## SAMPLE FIFTY MILLIGRAM SODIUM DIET (2644 calories)

			Prot. (gms)	Fat (gms)	CHO (gms)	Na (mgm)	K (mgm)
BREAKFAST							
ORANGE JUICE	100	grams	-	-	10	.5	190
OATMEAL	100	grams	2	-	15	2.0	170
TOAST (UNSALTED)	25	grams	2	-	15	1.0	18
BUTTER (UNSALTED)	10	grams	-	10	-	.5	.4
SODIUM-FREE MILK	240	grams	8	10	12	6.0	320
CASEC	15	grams	13.2	0.3	-	3.0	-
Subtotal			25.2	20.3	52	12.0	698.4
DINNER							
POTATOES	300	grams	6	-	45	2.4	1230
GREEN BEANS	100	grams	1	-	3	.9	300
BREAD	25	grams	2	-	15	1.0	18
BUTTER	30	grams	-	30	-	1.5	1.2
SODIUM-FREE MILK	240	grams	8	10	12	6.0	320
COCA-COLA	120	grams	-	-	11.4	1.2	62
TOMATO SALAD	50	grams	-	-	-	1.5	115
ORANGE	100	grams	-	-	10	.3	170
CANNED PEACH	100	grams	-	-	20	5.0	31
CASEC	15	grams	13.2	0.3	-	3.0	-
Subtotal			30.2	40.3	116.4	22.8	2247.2
SUPPER							
BEAN SOUP	300	grams	5	-	15	1.0	1300
MACARONI	300	grams	19.5	1.9	114	1.5	240
BREAD	25	grams	2	-	15	1.0	18
BUTTER	10	grams	-	10	-	.5	.4
SODIUM-FREE MILK	240	grams	8	10	12	6.0	320
COCA-COLA	120	grams	-	-	11.4	1.2	62
GREEN PEPPERS	as desired		-	-	-	-	-
CUCUMBER	50	grams	-	-	-	.5	115
BANANA	100	grams	-	-	20	.5	420
PEARS (RAW)	100	grams	-	-	15.8	2.0	100
CASEC	15	grams	13.2	0.3	-	3.0	-
Subtotal			47.7	22.2	203.2	17.2	2575.4
TOTAL			103.1	82.8	371.6	52.0	5521.0
			(milliequivalents			2.2	141.5

Supplemented with iron and vitamins



TABLE APP.-XVI

## OTHER CONSTITUENTS WHICH MAY BE USED IN A FIFTY MILLIGRAM SODIUM DIET

BEVERAGES:	COCA-COLA, FRUIT JUICES, SODIUM-FREE DIALYZED MILK, WATER
CEREALS:	Cooked: CREAM OF WHEAT(PLAIN), CORN MEAL, OATS(ROLLED), RALSTON, WHEATENA Dry: PUFFED RICE, PUFFED WHEAT, SHREDDED WHEAT
FRUIT:	ANY FRESH FRUIT EXCEPT CANTALOUPE Canned: APPLESAUCE, APRICOTS, CHERRIES, GRAPES, PEACHES, PEARS, PINEAPPLE, PRUNES, DATES, FIGS, (RAW OR CANNED), LEMON JUICE
MISCELLANEOUS:	BREAD(UNSALTED), BUTTER(UNSALTED), CASEC, CINNAMON, CLOVES, COCOA(Hershey), COCONUT(FRESH OR UNSALTED), CORNSTARCH, FLOUR, HONEY, JELLY, MACARONI, MUSTARD, NECCO WAFERS, NUTS(UNSALTED), PEANUT BUTTER(UNSALTED), PEPPER(BLACK), POPPED CORN(UNSALTED), VINEGAR, SPAGHETTI, SPRY, SUGAR
VEGETABLES:	ASPARAGUS(FRESH OR FROZEN), BEANS(DRY NAVY, FRESH OR FROZEN GREEN, FRESH LIMA, SOY), CORN ON COB (FRESH), CRANBERRIES, CUCUMBERS, EGGPLANT, LENTILS, LETTUCE, ONIONS, PEAS(FRESH), PEPPER(GREEN), POTATO, TOMATO, RICE

Variety has been added to the diet by use of readily available proprietary handbooks describing the use of protein supplements modified when necessary by eliminating those ingredients that would increase the sodium content of the diet above fifty milligrams.

All foods to be cooked without addition of salt.  
This diet must be supplemented with iron and vitamins.

TABLE APP.-XVII

## LOW SODIUM DIET-APPROXIMATELY 200 MGM.

BEVERAGE	LOW SODIUM MILK (2 CUPS)
	TEA
	FRUIT JUICE
	COCA COLA
	COCOA (American PROCESS) MADE WITH LOW SODIUM MILK OR WATER
BREAD	YEAST BREAD OR ROLLS, MADE WITHOUT SALT OR MILK AS DESIRED
CEREAL	COOKED WITHOUT SALT - AS DESIRED
	PUFFED WHEAT
	PUFFED RICE
	SHREDDED WHEAT
FAT	ANY UNSALTED FAT, AS DESIRED
FRUIT	AS DESIRED (LIMIT CANTALOUPE AND DRIED FIGS TO ONE SERVING)
MEAT or alternate	EGG - LIMIT TO ONE A DAY
	MEAT OR FISH - 5 OUNCES COOKED WEIGHT
	ANY FRESH MEAT, EXCEPT KIDNEY, LIVER
	ANY FOWL
	ANY FRESH FISH
	OYSTERS
POTATO or alternate	AS DESIRED
SEASONING	ANY EXCEPT SALT
SOUPS	CREAM SOUPS, MADE FROM ALLOWED FOODS
DESSERTS	MADE FROM ALLOWED FOODS, SUCH AS UNSALTED FRUIT PIE, FRUIT TAPIOCA, CORNSTARCH PUDDING
SWEETS	JAM, JELLY, HONEY, MAPLE SYRUP, WHITE SUGAR, AS DESIRED
VEGETABLES	1 CUP OF FRESH OR FROZEN OR CANNED WITHOUT SALT:
	ASPARAGUS
	BROCCOLI
	COW PEAS
	GREEN BEANS
	BRUSSEL
	EGGPLANT
	WAX BEANS
	CABBAGE
	ENDIVE
	FRESH LIMA BEANS
	CARROTS
	LENTILS, DRY
	NAVY BEANS
	CAULIFLOWER
	SQUASH
	PEAS, FRESH
	RUTABAGAS
	CORN
	TOMATOES
	TURNIPS
	LETTUCE
	SOY BEANS
	PARSLEY
	PARSNIPS

1. No salt, soda or baking powder used in the preparation of any foods.
2. No meat juices, broths, or gravies are to be used.
3. Frozen lima beans and peas are salted.

## TABLE APP.-XVIII

## LOW SODIUM DIET APPROXIMATELY 800 MG.\*

This diet is a general diet except that no salt, soda, or baking powder is used in the preparation of any food.

Milk, eggs, meat and fish are relatively high in sodium, so should not be served in larger than standard servings.

BEVERAGE	ANY KIND, UNSALTED
BREAD	YEAST BREAD (MADE WITHOUT SALT)
CEREAL	ANY CEREAL COOKED WITHOUT SALT PUFFED RICE PUFFED WHEAT SHREDDED WHEAT
DESSERT	ICE CREAM PUDDING (UNSALTED) CUSTARD GELATINE DESSERT FRUIT WHIPS SPONGE AND ANGEL CAKE (UNSALTED) PIE (UNSALTED)
FAT	ANY UNSALTED FAT
FRUIT	ANY FRUIT
MEAT or alternate	UNSALTED COTTAGE CHEESE, FISH OR MEAT; EGGS
POTATO or alternate	MACARONI, SPAGHETTI, NOODLES RICE, POTATO
SEASONING	ANY EXCEPT SALT
SOUP	CREAMED SOUP FROM ALLOWANCE
SWEETS	HONEY, SYRUP, SUGAR, JELLY AND JAM
VEGETABLE	ANY FRESH OR FROZEN OR CANNED WITHOUT SALT

EXCLUDE the following foods:

1. Salted, smoked and prepared meats; any cheese except cottage; meat gravies; and meat broth.
2. All commercially canned vegetables, relishes, and salad dressing, unless prepared without salt.
3. Frozen lima beans and peas are salted.

\* 800 mgm. sodium equals 2 gm. NaCl.



TABLE APP.-XIX

## NEUTRAL ASH DIET

FOOD	AMOUNT	ACID	ALKALINE
MILK	720 cc		15
ORANGE JUICE	200 cc		9.6
OATMEAL	30 gm	4.8	
BREAD	180 cc	10.2	
EGGS	2	11.0	
BUTTER	-	-	-
SUGAR	-	-	-
CHICKEN	90 gm	9.6	
BEEF	90 gm	10.8	
GRAPEFRUIT	100 gm		4.2
APPLESAUCE	100 gm		2.4
POTATO	100 gm		9.0
CARROTS	100 gm		13.5
CORN	100 gm	2.0	
RICE (DRY)	30 gm	2.8	
GRAHAM CRAX	2	2.2	
TOTAL		53.4	53.7

TABLE APP.-XX

NUMBER OF MILLIGRAMS OF VARIOUS IONS PER 100 CC. PROVIDING  
ONE MILLIEQUIVALENT PER LITER

Ion	Atomic or Radicular Weight	Valence	No. of mg./100 cc. Providing 1 mEq/l.
Hydrogen [H <sup>+</sup> ]	1.008	1	0.10
Sodium [Na <sup>+</sup> ]	22.997	1	2.30
Potassium [K <sup>+</sup> ]	39.096	1	3.91
Calcium [Ca <sup>++</sup> ]	40.08	2	2.00
Magnesium [Mg <sup>++</sup> ]	24.32	2	1.22
Chloride [Cl <sup>-</sup> ]	35.457	1	3.55
Bicarbonate [HCO <sub>3</sub> <sup>-</sup> ]	61.018	1	6.10
Biphosphate [H <sub>2</sub> PO <sub>4</sub> <sup>-</sup> ]	96.996	1	9.70
Phosphate [HPO <sub>4</sub> <sup>=</sup> ]	95.988	2	4.80
Bisulfate [HSO <sub>4</sub> <sup>-</sup> ]	97.074	1	9.71
Sulfate [SO <sub>4</sub> <sup>=</sup> ]	96.066	2	4.80



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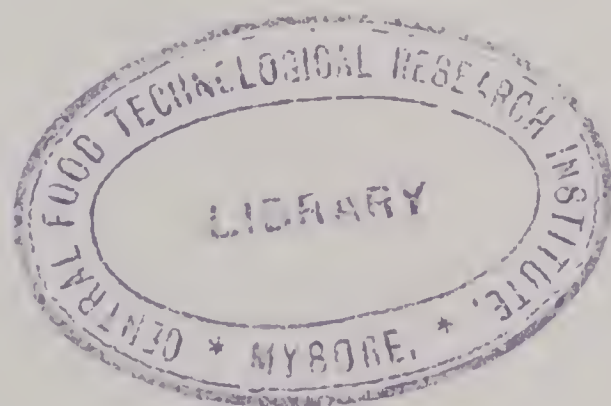
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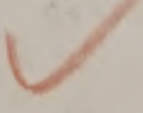
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